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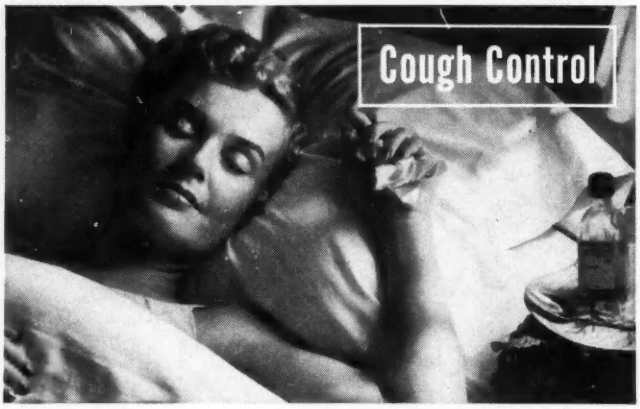

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Diagnosis of Pulmonary Coccidioidal Infections

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SUMMARY

A wide variety of pulmonary lesions may be caused by coccidioidomycosis. Suspicion of coccidioidomycosis may be substantiated by careful clinical-epidemiological histories. The first laboratory procedure should be a coccidioidin skin test. If the reaction to the test is positive, serological tests are next. Also, if there is no reaction to coccidioidin, serological tests are still indicated if dissemination is suspected. The more severe the infection, the greater the probability of establishing a diagnosis serologically. In only three-fifths of patients with coccidioidal cavities can the diagnosis be fixed serologically. In such patients if differential skin tests are not conclusive, attempt should be made to recover the fungus. However, this is accompanied by great risk of laboratory infection. Eosinophilia and accelerated erythrocyte sedimentation are only circumstantial items of evidence, as is the appearance of the pulmonary roentgenogram.

COCCIDIOIDOMYCOSIS enters the differential diagnosis whether a pulmonary lesion is discovered during the course of clinical illness or as the consequence of routine or mass x-ray surveys. In either event clinical and epidemiological histories are the first steps in ariving at the diagnosis.

CLINICAL SPECTRUM

Approximately 40 per cent of naturally-acquired human coccidioidal infections are accompanied by symptoms.[27] Most common are pleurisy, fever, malaise, cough, anorexia, backache, and night sweats. Not infrequently toxic erythema also develops. The patient may be prostrated or he may have only transient malaise. The pleural pain may be so severe as to be mistaken for that of coronary occlusion, nephrolithiasis, cholecystitis or fractured rib, or it may be so mild as to be only a sensation of oppression or tightness in the chest. In some instances the headache of coccidioidomycosis has been attributed to brain tumor or poliomyelitis. The toxic erythema has been confused with measles or scarlet fever. Five per cent of infections in males and as high as 25 per cent[27] of infections in females are accompanied by erythema nodosum or erythema multiforme, often associated with arthralgia. The arthralgia has caused confusion with rheumatic fever. Coccidioidal erythema nodosum must be distinguished from other sensitizing causes such as primary tuberculosis, streptococcosis or drug reactions. However, it is a useful sentinel which even can be used as an index for estimating incidence of coccidioidal infections. The erythema multiforme, which occurs especially on the upper extremities, thorax and face, is more apt to cause confusion and on several occasions has led to a diagnosis of smallpox. Pleural effusion, which is occasionally "silent," is generally associated with the initial infection although where a peripherally-located coccidioidal cavity breaks into the pleural space, hydropneumothorax develops secondary to the bronchopleural fistula.[31] This complication gen-

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erally occurs months or years after the initial infection.

While coccidioidal dissemination usually occurs within a few months of the primary infection, a pulmonary lesion may not have been present or frequently has regressed so that the pulmonary roentgenogram is within normal limits when dissemination is diagnosed. It is noteworthy that dissemination occurs most frequently in dark-skinned males, in at least 1 in 100 infections of Negro males as compared with 1 in 400 of white males.[27] Dissemination is least frequent in white females except, as Vaughan suggested,[37] when infection is acquired during the last trimester of pregnancy.

Those are the highlights of the clinical spectrum of primary infection and the epidemiological aspects of disseminated coccidioidomycosis which provide for an index of suspicion.

An additional word should be said with respect to clinical history for coccidioidal pulmonary cavitation. As Winn[40] pointed out, most cavitations are "cyst-like" and silent. Hemoptysis frequently is associated with the condition, but rarely are the lesions progressive nor is the patient comparable to a person with either tuberculous cavitation or disseminating coccidioidomycosis.[31] Similarly, if a pulmonary lesion is proved to be a coccidioidal residual, the physician and patient can both relax. The difficulty is the exclusion of other diagnoses, especially tumor, since asymptomatic lesions detected by mass surveys usually cannot be proved to be coccidioidal unless they are found at a site previously known to have been involved in coccidioidal pneumonitis.

RESIDENCE HISTORY

While the clinical history mainly serves to alert the physician to the possibility that a pulmonary lesion is coccidioidal, a careful residence history frequently provides extremely significant evidence. Of course, persons residing in known endemic areas always are suspect, and for those living outside such areas a history of transient exposure as in touring by automobile or train is a very valuable clue. The author has records of three persons who were infected merely as tourists on trains and of 13 others who were exposed only in riding through an endemic area by automobile or bus. With the knowledge that the incubation period is seven to 28 days, generally 10 to 16 days, it is often possible to fix the time of coccidioidal infection quite firmly by careful interrogation. Of course, the more exotic exposures to dusty products, even human fomites, must not be overlooked and rare cases are encountered in which no residence exposure can be traced. Especially should one be on the lookout for the laboratory-acquired infection.[20, 34] It is axiomatic that unless the most extraordinary facilities are available, whenever Coccidioides is handled on solid media not only the laboratory technician wielding the loop but also those in the environment may become infected. However, as the endemic area is not often thus brought to the patient, it is well to be familiar with the known geographical distribution of Coccidioides.

Several reviews[1, 22, 23, 29] have indicated the endemic areas. Outside North America, Coccidioides has long been recognized in Argentina. Recently Venezuela[3] and the Paraguayan Chaco[9] have been added. While cases have been attributed to Italy, the Balkans and Hawaii, none have been consistently reported from those areas. Those odd cases reported from China and Canada are erroneous. Certainly, the northern states of Mexico are endemic areas. Within the United States of America (Figure 1) beginning at Mission, Texas, the entire Rio Grande Valley westward is involved. The area extends northward spottily around San Antonio but certainly surrounds San Angelo. It stops south of Wichita Falls. The area extends westerly past El Paso into New Mexico. The southern part of New Mexico is involved, but Albuquerque, Santa Fe and all northern New Mexico are spared. Southern and Central Arizona are highly endemic, including both Tucson and Phoenix. At Florence 50 per cent of susceptibles are infected within six months. Northern Arizona is nonendemic, but the regions around St. George in Utah and Las Vegas in Nevada seem to be mildly endemic.

ENDEMIC AREAS IN CALIFORNIA

In California the most famous area is the San Joaquin Valley. In its southern reaches, 25 per cent of susceptibles may be infected annually.[28] The endemicity, as gauged by the incidence of the disease, diminishes from there northward. Near Hanford the incidence is one-half the Bakersfield rate. While as far north as Chowchilla there is a considerable incidence, Merced, only 20 miles farther north on Highway 99, has very few cases. Along the eastern side of the valley the incidence is very spotty in Merced and Stanislaus counties. However, along the west side it extends through Vernalis nearly to Tracy. One or two isolated cases have been noted in Yolo and Contra Costa counties, but there is no really proven endemicity in the Sacramento Valley. The area does extend over the Coast Range into San Benito, Monterey and San Luis Obispo counties. The region around San Miguel (Camp Roberts[24]) and Paso Robles is endemic but the city of San Luis Obispo is not. The westerly portions of Santa Barbara and Ventura counties (to Fillmore) are endemic, as is the northern part of Los Angeles county, apparently including at least the upper portion of the San Fernando Valley. There is spotty endemicity[38] in Riverside and San Bernardino counties as well as San Diego County.[29] More than a year ago Kessel reported on the endemicity of Southern California,[18] and additional delimitation of the area will be important. However, this sketch should recall the clues arising from geographical association. Epidemiological assistance also can come from data with respect to seasonal exposure to the dusty summer and fall or to dust storms. It should be borne in mind, moreover, that even soon after a winter rainstorm, dust frequently blows. Thus, some infections also occur during the rainy season.[25, 28]

Figure 1.—Known coccidioidal endemic areas in the United States of America. (Permission to reproduce outline map by University of Chicago Press.)

ESSENTIAL LABORATORY PROOF

While clinical and epidemiological histories may arouse suspicion and provide supporting evidence, proof that a pulmonary lesion is coccidioidal depends upon laboratory evidence.

Coccidioidin Skin Test

The first procedure should be the coccidioidin skin test. The history of the development of the coccidioidin test has been given in detail.[30] Suffice it to say that Cummings,[6] Davis,[7] Hirsch, Benson and D'Andrea,[10-11] Jacobsen,[13] Beck,[2] Eddie,[12] Kessel[16] and Stewart[35] are some of those to whom great credit is due for developing this very useful test. Now available commercially,* coccidioidin is generally used in 1:100 dilution of a Berkefeld filtrate of multiple cultures of Coccidioides grown on asparagine synthetic medium.

It does not activate old, quiescent infection, nor is the currently provided material antigenic.[30] Therefore, unlike brucellergin, it does not sensitize. Neither does coccidioidin evoke humoral antibodies and interfere with coccidioidal serological tests. While a severe reaction may cause local discomfort and occasionally evoke fever and malaise, there is no focal reaction. The only significant systemic complication which may occur is exacerbation or precipitation of erythema nodosum or erythema multiforme in association with a primary infection.

The result of an intradermal coccidioidin test should be observed at 24 and 48 hours. Induration greater than 5 mm. in diameter should be considered a positive reaction. As the active principle of coccidioidin is mainly carbohydrate, it is quite stable, which probably also accounts for its lack of antigenicity. Kept refrigerated and uncontaminated, even in 1:100 dilution it remains potent at least two years. Care must be taken not to use syringes which have contained other biologic materials unless the equipment is soaked overnight or boiled in dichromate cleaning solution.

The significance of the results of the coccidioidin test are comparable to those of the tuberculin test. The test is diagnostic only when an initial negative result early in infection is followed by a positive reaction upon repeat of the test later — so-called "conversion." In one-sixth of uncomplicated primary infections, 1:100 coccidioidin evokes no reaction during the first week of infection (Chart 1); but unless there is dissemination, there is invariably positive reaction by the fourth week. Thus "conversion" may be diagnostic. Moreover, in endemic areas if tests are repeated every six months, the test provides the most sensitive index of infection.[27, 28] Generally, it can only serve as a screen. However, if the subject tested has merely traveled through or resided a short time in an endemic area, logically a positive reaction can be considered very significant. Moreover, when erythema nodosum is suspected to

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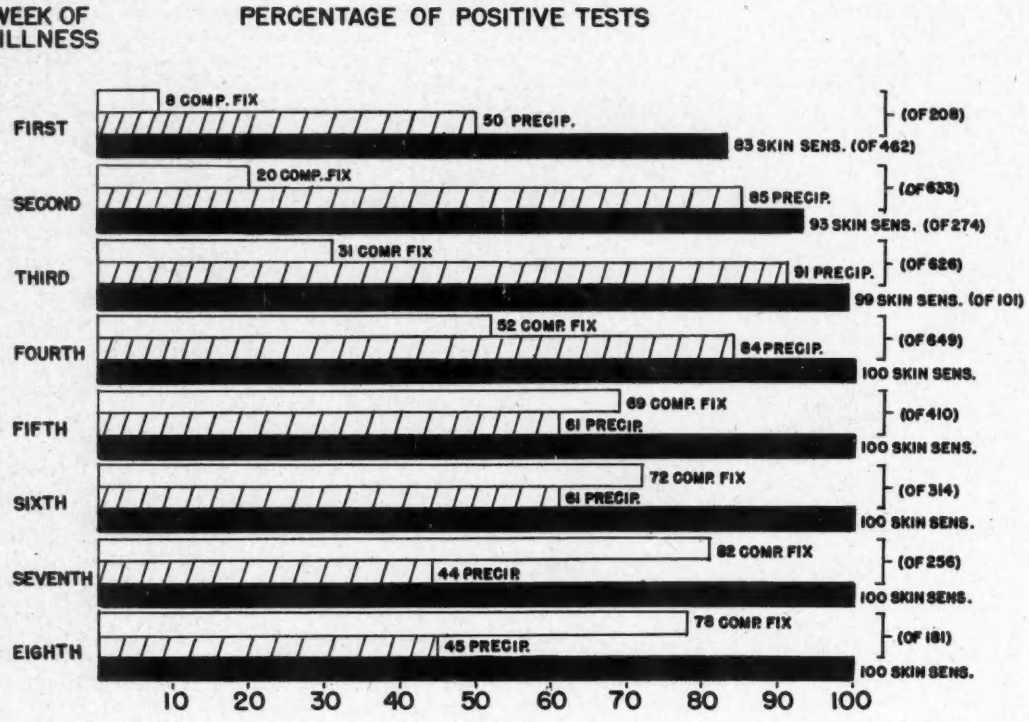
Chart 1.—Percentage distribution of positive precipitin and complement-fixation tests in sera and 1:100 coccidioidin tests in skin of patients with primary non-disseminating coccidioidomycosis (by weeks of illness).



be coccidioidal, a negative result eliminates that diagnosis since the skin lesions are themselves manifestations of hypersensitivity.[25]

Skin tests may differentiate between tuberculous and coccidioidal pulmonary lesions. Not infrequently pulmonary cavities or residuals have been established as coccidioidal when the result of a tuberculin test proved negative.

However, when a patient's infection is disseminated or an extrapulmonary lesion already has developed, there may be no reaction even to undiluted coccidioidin.[31] Moreover, there is association between sensitivity and favorable prognosis of disseminated infection, between anergy and poor outlook.

Dermal sensitivity generally persists for many years. However, sometimes it wanes and occasionally persons with coccidioidal cavities may have no reaction to coccidioidin more dilute than 1:10, and very rarely may not react to material even in that concentration.[30] That this is not the result of failure of antigenic "coverage" has been noted in several instances, when results of skin tests were negative but coccidioidin from the same strains fixed complement in the sera of the same patients. Coccidioidin in concentration of 1:10 or more must be used cautiously, for non-specific reactions may occur.[32] Coccidioidin does not cross-react with bacterial, viral or rickettsial infections; occasionally there have been cross-reactions noted with other mycotic antigens, notably haplosporangin, histoplasmin and blastomycin.[8, 26, 29, 32] Histoplasmin is more apt to cross-react in coccidioidal infections than coccidioidin in those dominantly sensitive to histoplasmin. However, when the antigens are used in balance, there is rarely difficulty in ascertaining which infection is dominant.[17, 18, 19, 32] Moreover, history of residence in the Mississippi Valley or the tropics can usually aid in fixing dominant histoplasmin sensitivity.

Serological Tests

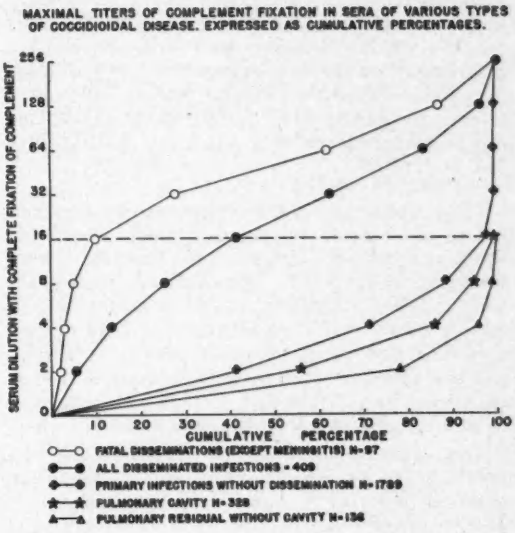
If coccidioidin sensitivity has been demonstrated, or if the test result is negative but the patient is suspected to be undergoing coccidioidal dissemination or has a very thin-walled, "nonreactive" cavity and an accusative residence history, serological tests come next.[33] If a patient is merely undergoing a respiratory illness suspected to be coccidioidal, serological tests should be deferred until "conversion" of the coccidioidin test to positive takes place. The diagnostic humoral antibodies develop more slowly than dermal sensitivity (Chart 1). Thus, while only one-sixth of the patients with uncomplicated primary infections have no reaction to 1:100 coccidioidin in the first week of the disease, fully one-half of those who ultimately will become serologically positive do not have precipitins and nine-tenths do not have complement-fixing antibodies so early. If

the skin test reaction becomes positive, serological tests may be requested. If combined precipitin and complement fixation tests are done repeatedly in patients with coccidioidal disease so severe as to require hospitalization, the results will be diagnostic in over nine-tenths of cases. If dissemination occurs, the reaction to these tests is positive in over 99 per cent of cases. The tests are diagnostic in approximately three-fifths of cases in which there is coccidioidal cavitation. They are seldom positive in patients with asymptomatic pulmonary residuals, but qualify as appropriate "long shots."

The methods of carrying out these serological tests and interpreting them have been described in detail.[33] In precipitin tests, made with a constant quantity of serum and increasing dilutions of appropriate antigen, the results are indicated by buttons which develop over a period of five days. In a series of over 3,200 positive serological tests in patients with non-disseminating primary infection, precipitins alone were positive in 44 per cent. Thus, the test is important where the acute phase of infection is suspected. It must be reiterated that serological tests should be withheld until the skin tests convert. The precipitin antibodies begin reverting in the third week of the disease and seldom persist longer than four months. The complement fixation test is done with serial dilutions of serum as in any quantitative Kolmer test.[17, 33] Positive reaction may continue into the third month (Chart 1) but in some cases reversion begins in the second month. Complement fixation may persist for several years, even with uncomplicated infections. When dissemination has occurred, even after recovery it may continue indefinitely. However, even when there is a residual pulmonary lesion or cavity formation, after several years the results of serologic tests are frequently entirely negative or equivocal. Thus when an acute, pneumonic-type illness is suspected as coccidioidal, both precipitin and complement fixation tests are appropriate. With more long-standing infections, especially for the diagnosis of old asymptomatic pulmonary residuals or cavities, only complement fixation tests need be done.

The titer of complement fixation correlates with the severity of the coccidioidal infection (Chart 2). Thus two-fifths of nearly 1,800 patients with uncomplicated primary infections whose sera fixed complement had titers no higher than the first dilution (1:2) while only one-fortieth had titers exceeding 1:16. Over half of 328 patients with coccidioidal cavities whose sera fixed complement had a titer of only 1:2 while only one in a hundred exceeded 1:16. In contrast three-fifths of over 400 patients with disseminating infections had titer over 1:16 and nine-tenths of approximately 100 patients with extensive, fatal disseminating infections exceeded that level. Negative results of serologic tests do not eliminate Coccidioides as the cause of a residual pulmonary lesion with or without cavitation. However, progressive coccidioidal pulmonary disease can usually be excluded if results are negative. The author has records of many cases of patients with primary or

CHART 2



metastatic pulmonary malignant disease or with tuberculosis in which suspicion of coccidioidomycosis could be eliminated because of negative results of serologic tests. Of course, diseases may coexist, so positive reaction to tests for coccidioidal infection does not necessarily eliminate concomitant tuberculosis or cancer from consideration. However, serial tests have given clues. When pulmonary lesions increase depite stable or falling serological titers, an additional non-coccidioidal cause is virtually certain.

Commercial provision, in the near future, of antigens for precipitin and complement fixation tests and the positive control serum requisite for the latter is probable.

Culture; Isolation of Coccidioides

Demonstration of Coccidioides is irrefutable proof of coccidioidal infection. Even during the acute primary infection a patient may not raise sputum. Unfortunately, with asymptomatic coccidioidal pulmonary residuals, results of sputum and gastric cultures are characteristically negative. The most damning objection to sputum cultures is the hazard of laboratory infections.[34] As was mentioned previously, handling of cultures on solid media almost inevitably results in laboratory infections. Coverslip examinations of sputum are safe but notoriously uncertain. The "spherules" (sporangia) with endospores may be missed or artifacts may be "identified" as Coccidioides. Culture on malt, Sabouraud's agar, or differential media[26] with inoculation of material from suspicious cultures intraperitoneally into white mice or intraperitoneally or intratesticularly into guinea pigs is necessary to complete identification as Coccidioides.

It must be admitted that in certain instances there is no substitute for culturing. For instance, in pa-

tients with pulmonary cavitation when results of both tuberculin and coccidioidin tests are positive and of serologic tests negative or equivocal, only recovery of the etiological agent will establish the diagnosis. In such circumstances the best procedure is to make cultures and, if suspicious growth occurs, to send the specimen to a place where subcultures can be made with safety.

Hematological Studies

Of accessory aid in the evaluation of pulmonary lesions are counts of leukocytes in the blood and determination of the erythrocyte sedimentation rate. During the acute illness eosinophilia can rise as high as 89 per cent.[39] Polymorphonuclear leukocytosis in the region of 10,000 to 14,000 with a high proportion of banded forms is frequent early in the illness, and this phenomenon is usually succeeded by lymphocytosis. In patients with coccidioidal cavities or pulmonary residuals the leukocyte count is normal.

The sedimentation rate usually is accelerated during "active" infection. Slowing of the rate is an index of recovery. A normal sedimentation rate in nearly three-fourths of 150 cases of coccidioidal cavitation has been reported[31]—further evidence that in most of such cases the infection is quiescent.

ROENTGENOGRAMS

Roentgenographic evidence may cause suspicion of a coccidioidal pulmonary lesion. Extensive descriptions[4, 5, 14, 15, 21, 31, 36, 40] of the various coccidioidal lesions in the lungs have been presented. However, roentgenograms can never establish the diagnosis. Radiologists with long experience may be correct nine times out of ten, and with thin-walled coccidioidal cavities may score even higher. However, as with a well-nigh indicting residence history, the diagnosis still depends upon other laboratory means.

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Some Recent Advances in Thoracic Surgery

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SUMMARY

In this brief presentation of some recent advances in thoracic surgery a number of miscellaneous topics which deserve consideration at this time are discussed. Among these are acidosis during anesthesia for thoracic operations, the problem of esophagitis in relation to surgery, recent improvements and reorientations in pulmonary operations, and some comments on operations upon the heart and great vessels.

IN a consideration of recent advances in thoracic surgery the great contributions of allied fields which have made these achievements possible immediately come to mind. The development of anesthesiology has permitted long and detailed transpleural operations. Antibiotics have radically changed the indications, the timing of operative intervention, and the postoperative morbidity. Adequate blood replacement and improved preparation and postoperative care have played an important role. Fundamental advances in physiologic knowledge have been made.

It is well known that some so-called advances of yesteryear have, with further observation, been shown to have their less favorable aspects. Especially when a surgical procedure entails an alteration in normal anatomical relationships or a disturbance of physiologic mechanisms, one may fail to foresee some late undesirable consequences. Therefore some of the topics to be mentioned briefly here are concerned with such problems which require attention at present.

ANESTHESIOLOGY

It is amazing that it has taken so long to recognize the vast importance of well conducted anesthesia in surgery. Probably relatively few physicians even today are fully aware of the many ways in which minor disturbances in respiration, circulation, and metabolism during anesthesia can influence morbidity and mortality. The secondary effects of abnormal ventilation or altered cardiocirculatory function are not limited to the first day or two after operation but may set the stage for other later complications.

One of the notable advances in anesthesiology in recent years has been in lessening the risk of hypoxia. But with the anesthetist's achievement of a quiet operative field for prolonged and meticulous intrathoracic operations, another problem has assumed greater importance — the carbon dioxide accumulation with resultant severe respiratory acidosis which is now known to be a common and undesirable occurrence. Pronounced retention of carbon dioxide in the anesthetized patient may cause little or no hyperventilation and usually does not produce transient hypertension as has been taught. Respiratory acidosis may be unrecognizable clinically but demonstrable by blood studies. The great importance of such respiratory acidosis lies in the fact that it increases the vulnerability of the patient to drugs and hemorrhage. The incidence of cardiac arrhythmia, a major problem in operations on the heart, is related to this aberration. Correction of this abnormal situation is one of the important assignments facing anesthesiologists.

ESOPHAGUS

During recent years the feasibility of resection of long lengths of the esophagus for cancer with reestablishment of alimentary continuity by intrathoracic esophagogastrostomy has been demonstrated. The stomach can even be mobilized sufficiently to bring it up into the cervical region. But in some cases the pathologic process, especially if benign, may be such that resection of only a limited segment of the esophagus is necessary. In the past it was taught that end-to-end anastomosis of the esophagus after resection of even a few centimeters of the gullet was not feasible because of tension and poor supply of blood. Laboratory and clinical experience during the past few years, however, has demonstrated that with adequate mobilization and careful suturing technique partial esophagectomy with reestablishment of continuity by anastomosis of the esophageal ends is feasible in selected cases.

Recently much has been added to the understanding of esophagitis and acid-peptic ulceration of the lower esophagus. It is pertinent to note that the incidence of these lesions has been increased by complications of esophageal and gastric operations done for other reasons. Clinical and experimental data have forcibly demonstrated the great vulnerability of the lower esophagus to acid-peptic juice. The normal mechanism for preventing regurgitation of gastric contents into the esophagus consists of an intrinsic muscular mechanism in the walls of the esophagus and, even more important, the anatomic arrangement at the diaphragmatic hiatus. The angles at which the esophagus passes through the hiatus and enters the stomach, the esophagophrenic membrane, and the diaphragmic crus all have an effect. Whenever the esophagogastric junction is displaced above the diaphragm, either as a result of a sliding hiatal hernia or as a result of surgical intervention, the stage is set for esophagitis and ulceration, since the

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diaphragmatic barrier to reflex has been removed. Esophagitis is not necessarily prevented by vagotomy. Therefore the surgeon would wisely not interfere needlessly with a normal esophageal diaphragmatic hiatus and should leave the entire stomach below the diaphragm whenever this is possible.

It is well known that many patients with esophageal hiatus hernia are asymptomatic. It is important to differentiate those patients with a paraesophageal hiatus hernia where the esophagogastric junction remains below the diaphragm from those patients in whom the esophagogastric junction has moved into the chest. In the latter type of sliding hernia, symptoms and esophagitis are much more likely to be present. The treatment of the esophagitis secondary to hiatal hernia is the surgical correction of the hernia through a transthoracic approach.

The primary treatment of so-called cardiospasm is peroral dilatation. If this proves inadequate, surgical intervention may be indicated, but any operative procedure which results in free regurgitation of gastric contents into the esophagus may eventually lead to a worse situation than the original condition. The simple procedure of cardiomyotomy is the operation of choice.

Recent clinical evidence has demonstrated that most cases of so-called congenital shortening of the esophagus are primarily sliding hiatal hernias with secondary esophagitis. It is surprising how short an esophagus may appear on the roentgenogram and still be stretched to its original full length by the surgeon, provided the esophagitis has not been present too long.

LUNGS AND PLEURA

In the last few years there have been continued advances in operations on the lungs and pleura. Antibiotics have had a profound influence. The thoracic surgeon has aimed more at conserving pulmonary function as well as further lowering morbidity and mortality.

The incidence of pulmonary abscess has been lowered by antibiotic treatment of early inflammatory processes. The management of a pulmonary abscess consists of intensive antibiotic treatment in the acute stage, and, if healing does not occur, surgical excision of the permanently damaged part of the lobe or lung.

Pulmonary resection plays an important role in the treatment of bronchiectasis. The development of surgical techniques which permit the removal of any individual or combination of pulmonary segments has permitted more conservation of pulmonary tissue and further extension of surgical treatment in cases of bilateral lesions.

Many articles have been written on the surgical treatment of so-called cystic disease of the lung. A review of the literature indicates much confusion because of inadequate correlation of clinical and pathological features. Many such lesions are well treated surgically, but it is important that localized obstructive emphysema, such as follows staphylococcus pneumonia in infancy and childhood, not be subjected to surgical excision, since such lesions usually disappear spontaneously.

The results of surgical treatment of benign pulmonary tumors have been excellent. Most neoplasms of the lung are malignant, however, and in this group the late results are very poor. Although the risks of surgical treatment are small, relatively few patients are operated upon while the disease is limited to the lung. Physicians must recognize that almost any undiagnosed shadow in the lung, even though the patient is entirely asymptomatic, may be a bronchogenic carcinoma. Exploratory thoractomy, and not merely observation, is the indicated program for the undiagnosed density in the lung. Fear that the lesion might be tuberculous is no longer a valid reason for delay.

Great strides have been made in recent years in the surgical treatment of tuberculosis. Surgical excision of portions of or the entire lung for pulmonary tuberculosis are now commonplace. Streptomycin has undoubtedly been very important in reducing the risks and increasing the scope of such operations. Today various collapse procedures, especially thoracoplasty, as well as the newer more direct surgical measures like resection are to be considered in conjunction with general medical treatment. Tuberculous empyema, a dreaded complication in the past, can now be treated with far better results by the combination of chemotherapy and surgical removal of the infected pleural lining together with, if necessary, the diseased pulmonary tissue.

Decortication of the lung, although not a new operation, has really been developed during the past few years. It is now known that in most cases of clotted hemothorax, long-standing pneumothorax, and empyema the thick layer which overlies the visceral pleura can be removed surgically, and thus expansion of the lung can be obtained provided that intrapulmonary disease does not prevent such reexpansion. If the underlying lung is not diseased, reexpansion can even be attained after many years of collapse. The advantage of such restoration of pulmonary function is obvious.

When localized bronchostenosis is encountered without destruction of the lung distal to the obstruction, transthoracic bronchotomy and plastic procedure on the bronchus may avert lobectomy or pneumonectomy. Similar procedures on the trachea are a recent important development.

MEDIASTINUM

Since x-ray surveys have become common, many mediastinal masses have been detected in the asymptomatic stage. A correct diagnosis preoperatively is often not possible, but such lesions should be removed surgically unless a real contraindication to operation exists. Even in some cases of bilateral hilar lymphadenopathy, exploratory thoracotomy is indicated in order to establish a positive diagnosis.

That respiratory difficulty in infancy and childhood may be caused by tracheal compression from anomalous blood vessels has been recognized re-

cently. In any case of stridor in an infant, study of the esophagus with barium should be carried out in order to determine whether or not it is caused by a vascular ring around trachea and esophagus. Such a vascular compression can be relieved by operation.

HEART AND GREAT VESSELS

Cardiac tamponade, rather than hemorrhage, has been recognized for many years as the prime factor in the death of many patients with stab wounds of the heart. The experience of the past decade, however, has stressed the great value of immediate needle aspiration of the blood from the pericardium as a life-saving measure. Surgical intervention may also be necessary.

The advent of streptomycin has permitted an early surgical attack on tuberculous pericarditis with cardiac compression. By the combination of prolonged chemotherapy and relatively early surgical removal of the tuberculous and fibrotic constricting membrane, satisfactory results may be anticipated.

Studies by cardiac catheterization of patients with constrictive pericarditis have added to the understanding of the pathologic changes in this condition and should lead to better surgical treatment. The chief sites of constriction are not the same in all cases, and variations must be recognized. By cardiac catheterization studies it has been learned that patients with constrictive pericarditis often have increased pressure in the pulmonary artery. Such investigations combined with surgical experience have demonstrated the importance of thoroughly decorticating the left ventricle and not merely concentrating attention on the inflow area of the right heart and anterior aspect of the ventricles.

The surgical correction of patent ductus arteriosus is a well-known chapter in medical history. It should be borne in mind that the percentage of patients with a patent ductus who do not have a typical "machinery" murmur is higher than published reports have indicated.

The recent advances in the surgical treatment of congenital heart disease with cyanosis have aroused widespread interest. It should be recognized that the results of operations which increase the flow of blood to the lungs are not uniform because of such factors as the degree of overriding of the aorta in the tetralogy of Fallot. In a field of surgery as recently developed as this, many changes are to be expected. Direct operations on the pulmonary valve are a new advance. Pulmonary valvulotomy is undoubtedly the logical treatment for isolated pulmonary stenosis, but the place of this operation in the therapy of tetralogy of Fallot awaits further experience.

The surgical treatment of coarctation of the aorta has been another dramatic advance. In this connection the organization of blood vessel banks to serve as a ready source of supply, when vessel grafts are needed, should be mentioned.

The patient with severe mitral stenosis can now be improved by surgical freeing of the margin of the fused valve leaflets. That such an operation does not necessarily lead to significant mitral regurgitation has been demonstrated.

These are but a few of the many recent advances in the cardiovascular and other aspects of thoracic surgery.

Careful and continued "follow-up" of patients subjected to the newer surgical procedures is of extreme importance to the compilation of maximum information concerning the later results and consequences of such operations.

3 East 71st Street.

A Study of Small Bowel Tumors

With Special Emphasis on Clinical Aspects

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SUMMARY

Ninety-eight patients with 100 different tumors of the small bowel were studied. There were more malignant than benign tumors. Adenocarcinoma was the commonest lesion and the ileum the most frequent anatomical site of all tumors. Except for carcinoid tumors, the lesions were observed more often in male than in female patients. The average age of patients in this series was higher than that reported in most other series. Loss of weight, and abdominal pain were the most constant symptoms. Clinical syndromes of anemia and bleeding, small bowel obstruction, biliary obstruction, perforation with peritonitis, abdominal tumor, melanosis with small bowel polyposis, and cutaneous von Recklinghausen's disease with small bowel neurofibromatosis were encountered either alone or in combination.

In the group operated upon, a resection of the involved segment with end-to-end anastomosis was done when feasible. None of the patients operated upon before 1946 lived as much as five years after operation. The most common causes of death were extension of the primary tumor and metastasis, peritonitis due to perforation, associated bronchopneumonia, and hemorrhage.

THAT tumors may occur in the small intestine is a fact too often ignored. The purposes of this study are to emphasize this fact, to stress the importance of a complete investigation of the patient with digestive complaints, to enter a plea for earlier diagnosis and treatment, and to add to the literature a report on a series of 100 tumors of the small bowel observed in 98 patients during a 13-year period at the Los Angeles County Hospital.

The experience of any one surgeon in diagnosing and treating tumors of the small bowel is limited. As a result the mortality rate in such cases is higher than in cases involving tumors of any other part of the gastrointestinal tract. The low salvage rate, in view of the fact that many of these tumors are slow-growing and metastasize late, is undoubtedly influenced by the long duration of the disease before it is diagnosed and treated. If the cause of a digestive complaint is not determined in a thorough clinical investigation, exploratory laparotomy may be indicated. Exploration should include careful examination of the entire small bowel.

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REVIEW OF THE LITERATURE

The incidence of malignant tumors of the large bowel is reported as 3.66 per cent of all malignant lesions, and of the small bowel as 0.098 per cent.[21] Willis[24] reported a series of 17 carcinomas of the small bowel and 190 of the large—a ratio of approximately 1:11. In most reported series,[4, 7, 8, 15] it was noted that small-bowel tumors were more often malignant than benign. Spier[22] stated that 3 per cent of all gastrointestinal carcinomas and 60 per cent of intestinal sarcomas occur in the small bowel. After the appendix the small intestine is the most common site of carcinoid tumors.[12] Leiomyomas make up 1 per cent of all gastrointestinal tumors, and hemangiomas 0.3 per cent.[2, 13] One-half of all gastrointestinal lipomas occur in the small intestine.

Cattell[5] declared that although small-bowel tumors are relatively rare, the diagnosis should be considered when examination of the stomach and colon does not reveal a cause for abdominal pain or bleeding. Rouse[20] listed, as indications for special studies, melena or the persistent presence of occult blood in the stools with unexplained anemia, abdominal pain or tenderness, and altered bowel function. X-ray studies done by a skilled radiologist may determine the presence of the lesion in only 25 per cent of cases.[6] A long intestinal tube has been used to locate the site of bleeding and also to collect specimens for cytologic study, with promising results in a few cases.[23, 16] Cattell[5] recommended that if definite diagnosis is impossible by other means, exploratory laparotomy be carried out, with thorough investigation of the small bowel.

The operative mortality rate in small-bowel carcinoma is 44 per cent and the five-year survival rate less than 5 per cent.[9] Similarly, prognosis in lymphosarcoma is poor while in leiomyosarcoma it is fairly good.[10, 19] Carcinoid or argentaffin tumors in the small intestine are reported to metastasize in up to 52 per cent of cases and are usually considered to be of low-grade malignancy.[17] The poor salvage rate is undoubtedly due to the long duration of the disease before treatment is given. Shallow[21] recommended wide segmental resection of all malignant tumors of the small bowel except moderately advanced lesions in the ampullary region of the duodenum; for such lesions he advised radical pan-

creaticoduodenectomy. For benign small-bowel tumors the treatment recommended is that which is indicated by the nature of the complication—intussusception, volvulus, hemorrhage—which leads to the operative diagnosis of the lesion.[3, 19, 18]

ANALYSIS OF DATA

One hundred small-bowel tumors were observed in 98 patients, 62 males and 36 females, during a 13-year period from 1938 through 1950. Ninety of the patients were Caucasian, seven Negro, and one Oriental. Sixty-one of the tumors were malignant and 39 benign. Thirty-four of the malignant tumors were in males and 27 in females—a ratio of approximately 7:5. The majority of benign and malignant tumors occurred in patients in the seventh and eighth decades of life (Chart 1). This may be explained by the fact that many of the benign tumors were only incidental in patients dying of other causes. Furthermore, in a charity hospital the average age of patients is higher than it is in the ordinary private hospital.

Anatomical Location. One carcinoid tumor, one sarcoma, and 19 carcinomas occurred in the duodenum (Table 1); but, except for carcinoma, the greater proportion of malignant lesions were in the ileum. Benign tumors occurred with equal frequency in duodenum and ileum. All sectors of the small intestine were involved in two cases of benign tumor.

Annual Distribution of Cases. Small bowel tumors were recognized with greater frequency both at operation and at autopsy during the last five years, and particularly during the last two years, of the period studied (Chart 2). During the 12 months July 1, 1949, to June 30, 1950, there were 202 patients admitted with a diagnosis of malignant disease of the large bowel and 16 with a diagnosis of malignant lesion of the small bowel, or a ratio of 12.6:1. In this series, the neoplasms were discovered at operation in 34 instances. Autopsies were done in 79 cases, in 15 of which operation had been done.

TABLE 1.—*Anatomical Location of Tumors*

Lesion	Duodenum Supra-Ampullary	Duodenum Peri-Ampullary	Duodenum Infra-Ampullary	Jejunum	Ileum	Throughout	Totals
MALIGNANT		21		11	29		61
Carcinoma	6	11	2	2	7		28
Carcinoid		1		2	9		12
Sarcoma		1		7	13		21
BENIGN		14		9	14	2	39
Adenomatous polyps	6	1	2	3	5		17
Leiomyoma		2		4	3		9
Neurofibroma		2		....	4	1	7
Lipoma		1		....	1		2
Heterotopic pancreas		....		1	....		1
Hamartoma		....		1	....		1
Lymphangiectatic polyp		....		....	1		1
Multiple hemangiomata		....		....	....	1	1

Pathologic Types. The various kinds of tumors observed are listed, in the order of incidence in this series, in Table 2. Since adenocarcinoma was the most common malignant lesion and the adenomatous polyp the most common benign tumor, it is suggested that one may be precursor of the other.

Symptomatology. The average duration of symptoms (Chart 3) in carcinoma was 5½ months, in sarcoma 9½ months, in carcinoid tumor 19 months; and the average for benign tumors was 23 months.

Benign neoplasms of the small intestine rarely cause symptoms except as complications develop. This may largely be true of malignant tumors also.

CHART 1

Age Incidence

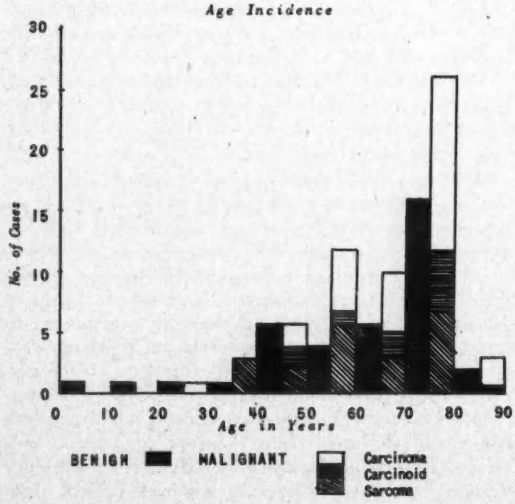

CHART 2

Annual Distribution of Cases

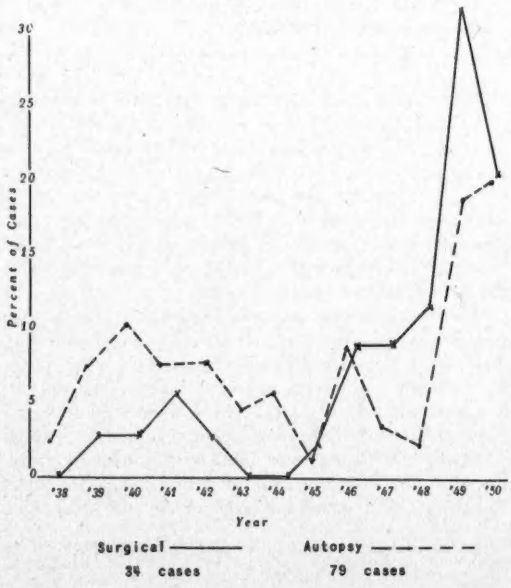

TABLE 2.—*Pathologic Types of Tumors*

Malignant		Benign	
Adenocarcinoma	28	Adenomatous polyps	17
Carcinoid	12	Leiomyoma	9
Lymphosarcoma	10	Neurofiroma	7
Leiomyosarcoma	7	Lipoma	2
Neurofibrosarcoma	3	Hamartoma	1
Melanoma	1	Heterotopic pancreas	1
		Lymphangiectatic polyp	1
		Multiple hemangiomata	1
Totals	61		39

In the present series the most commonly observed individual symptoms were loss of weight, pain, nausea and vomiting, and melena. Loss of appetite due to mechanical interference with the passage of food and the systemic effects of disseminated malignant disease resulted in loss of weight in 40 patients (Table 3). Although pain was a prominent symptom, it differed considerably because of the diversified etiologic factors. Vomiting, observed in 30 instances, might have been expected to occur more frequently, but the liquid content of the small bowel passes through remarkably small openings without producing obstruction.

Bleeding is more often occult in ulcerating mucosal tumors and massive in the cavitating, excavating connective tissue tumors of muscular origin.

Clinical Syndromes. Symptoms (Table 4) may be classified into one or more of the following syndromes: Bleeding with anemia, small-bowel obstruction, biliary obstruction, perforation with peritonitis, abdominal tumor, circumoral pigmentation with small-bowel polyposis, and cutaneous von Recklinghausen's disease with intestinal neurofibromatosis or leiomyomata.

Bleeding or anemia associated with melena, tarry stools, persistent occult blood on a meat-free diet, hematemesis (in three cases), and increasing weakness and fatigue was the commonest syndrome. In many cases, no abnormality was observed in roentgen studies of the large bowel and upper gastrointestinal tract with barium, and not infrequently the patients were considered neurotic.

Obstruction owing to a stenosing lesion or to acute or recurrent intussusception caused by a polypoid tumor, was the next most frequent symptom complex. Patients with symptoms of this order gave a history of variable duration of colicky abdominal pain, vague discomfort (often interpreted as "gas"), a change in bowel habit (usually constipation), and recurrent nausea and vomiting. It is significant that vomiting occurred in several cases without nausea.

Except for two cases, the syndrome of biliary obstruction occurred in association with lesions in the periampullary region of the duodenum. Bleeding with jaundice and pruritus, vague postprandial discomfort in the right upper quadrant of the abdomen and in the epigastrium, a palpable gallbladder, and occasionally nausea and vomiting were characteristic observations. In some cases the jaundice was intermittent but in the majority it was progressive.

Symptoms of peritonitis—severe continuous abdominal pain, rebound tenderness with rigidity, fever, and leukocytosis—may be the only manifestation of a perforating neoplasm in the small bowel. There may be associated symptoms of small-bowel obstruction. It should be remembered that elderly patients at times respond abnormally to peritonitis; in the present series a few had little or no abdominal pain and no leukocytic response to the disease.

An abdominal tumor was the primary symptom in two patients who complained of abdominal fullness and of a palpable "lump." There were a number of patients with other primary symptoms who also had a palpable tumor.

Less common, perhaps, but of interest are the last two syndromes listed in Table 4. In one patient in the present series the condition observed was like that described by Jeghers[14] — intestinal polyposis with melanotic spots on the oral mucosa, lips, and digits. This patient was twice operated upon for obstruction and a jejunal adenoma was removed on each occasion. Five patients with cutaneous von

CHART 3

Duration of Symptoms

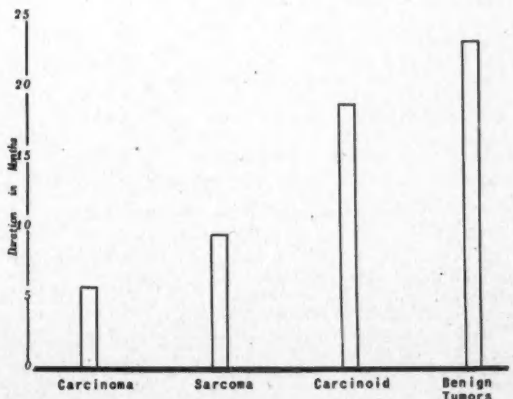

TABLE 3.—*Symptoms of Small Bowel Tumors*

Symptoms	Carcinoma	Carcinoid	Sarcoma	Benign Tumors	Totals
Weight loss	19	6	11	4	40
Pain	13	6	11	5	35
Nausea	7	2	7	2	18
Vomiting	12	5	8	5	30
Anorexia	5	1	4	1	11
Jaundice	9	....	1	1	11
Weakness	6	....	3	1	10
Constipation	5	....	6	2	13
Diarrhea	4	2	2	2	10
Melena	7	3	5	3	18
Hematemesis	2	2	....	....	4
Fever	2	3	1	1	7
Gas or Bloating	4	4	4	....	12
Hiccoughs	....	1	1	....	2
Pruritus	2	....	....	....	2

TABLE 4.—*Clinical Syndromes*

Bleeding with anemia (in 38 cases):
Melena, occult blood or tarry stools, hematemesis, weakness and fatigue

Small bowel obstruction (in 31 cases):
Incomplete and recurrent pain, nausea and vomiting, "gas," constipation

Biliary obstruction (in 14 cases):
Jaundice, pruritus, nausea and vomiting, vague right upper abdominal pain, palpable gallbladder

Perforation with peritonitis (in 15 cases):
Constant pain, tenderness with rebound rigidity, fever, leukocytosis

Abdominal tumor (in 3 cases):
Sensation of abdominal fullness or heaviness with or without digestive complaints

Melanosis with small-bowel polyposis (in 1 case)

Cutaneous von Recklinghausen's disease with intestinal neurofibromatosis (in 5 cases)

Recklinghausen's disease had similar lesions of the small bowel which were multiple in four cases. It is also noteworthy that in two cases of benign leiomyomata and in two of leiomyosarcomata there was an associated diagnosis of fibromyomata uteri.

DIAGNOSIS

In 16 per cent of the 62 cases in which symptoms were present, the lesion was correctly diagnosed; in 19 per cent the diagnosis was obstruction of the bowel, and in 8 per cent gastrointestinal malignant disease was diagnosed but the site of the lesion was not determined. In the remaining 58 per cent the diagnoses were incorrect. It should be mentioned that since many of the patients entered the hospital critically ill, an adequate study could not be done. Diagnostic measures included examination of stools for occult blood and parasites, upper and lower gastrointestinal barium studies, and small-bowel progress meals, proctosigmoidoscopy, gastroscopy, peritoneoscopy, and the use of a small-bowel tube to determine the site of obstruction. No one of these procedures was diagnostic in more than three cases, but it is only through the use of these studies in conjunction with a careful history and physical examination that diagnostic accuracy can be improved. As stressed before, if diagnosis cannot be confirmed otherwise, operation is indicated as a diagnostic as well as a therapeutic procedure.

TREATMENT

Thirty-four patients in this series were operated upon and malignant tumors were found in 78 per cent of them. En bloc resection with end-to-end anastomosis was done in 15 cases of malignant growth and five cases of benign lesions of the jejunum and ileum. Of the four patients with ampullary lesions of the duodenum, one was treated with local excision and three with resection of the Whipple type. Four patients were treated with side-tracking measures for palliation, and in three cases only exploration and biopsy were carried out. There were no five-year survivals among the eight patients operated upon before 1946.

Causes of Death. Thirty-four patients were operated upon, seven for benign and 27 for malignant lesions. Four of those with benign lesions are alive, while three of those with malignant disease had lived, at the time of this report, an average period of 21 2/3 months after operation. There were 13 postoperative deaths in the group with malignant lesion, while 11 survived the first two-week period for an average of 15 months.

The most common cause of death (Table 5) was recurrent disease with metastasis. Next in order were postoperative bronchopneumonia, peritonitis secondary to perforation, pulmonary embolism, postoperative bleeding, evisceration, infarction of bowel attributable to interference with blood supply. In three cases death was caused by unrelated disease. Only one patient with a benign tumor died as a result of direct complications of the tumor.

Autopsy was done in 36 cases of malignant tumors and 31 cases of benign lesion. A small-bowel tumor was an incidental finding in nine of the former and 27 of the latter group. The majority of patients with malignant tumor died as a result of the local disease and metastasis (Table 6). Peritonitis due to perforation, intercurrent bronchopneumonia, bowel obstruction, and massive hemorrhage, in order of frequency, were other causes of death.

DISCUSSION

Tumors of the small intestine are not rare, although compared with tumors of the lung, stomach, and colon they are not common. This was emphasized in this series in which the incidence of malignant tumors of the small intestine was one-twelfth the incidence of such lesions in the large intestine. Further, such tumors as sarcoma and lipomas more often involve the small intestine than any other part of the gastrointestinal tract.

TABLE 5.—*Causes of Death in Cases in Which Operation Was Carried Out*

	Malignant	Benign
Recurrent disease with metastasis	6	....
Postoperative bronchopneumonia	5	....
Peritonitis due to perforation	5	1
Pulmonary embolism	2	....
Postoperative bleeding	1	....
Small bowel infarction due to interference with blood supply	1	....
Unrelated disease	3	2
Totals	24	3

TABLE 6.—*Causes of Death (Autopsy Cases)*

	Malignant	Benign
Local disease with metastasis	14	....
Intercurrent bronchopneumonia	2	....
Peritonitis due to perforation	9	1
Bowel obstruction	1	1
Massive hemorrhage	1	1
Unrelated disease	9	27
Totals	36	30

This study indicates that where there is greater awareness of these lesions, they are diagnosed with greater frequency. Abdominal exploration should include a systematic study of the entire small bowel; even then, soft polyps may be overlooked.

In cases of malignant disease of the small intestine, the salvage rate in this series was exceedingly small. This is explained in part by the duration of symptoms prior to the establishment of diagnosis and treatment. Durations of symptoms of five and one-half months for carcinoma and nine and one-half months for sarcoma and 19 months for carcinoid tumors prior to treatment are dangerously long.

Many factors are responsible for the delay. Physicians are accountable for some of it. Symptomatic treatment of dyspepsia with incomplete diagnostic study is a poor approach to the problem of carcinoma of the small intestine. In approximately one-third of the cases in this series, treatment was begun only after the precipitous onset of major complications. It is obvious, then, that the earlier operation is done, the greater the opportunity to deal with uncomplicated local disease, and the higher the salvage.

Since many of the patients were admitted in a condition necessitating emergency operation, any attempt at complete diagnosis was impossible. On the other hand, in cases in which the patient has symptoms of chronic dyspepsia or recurring cramping abdominal pain, yet the routine x-ray studies of the stomach, gallbladder, and colon do not supply a definite clue, the small bowel must be examined carefully by x-ray. If any doubtful lesion is observed, it should be investigated further with selective x-ray and cytologic studies, utilizing the long intestinal tube.

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The Physician and the Atomic Bomb

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SUMMARY

Atomic detonations are essentially of two types: contaminating and non-contaminating. The only non-contaminating burst is the high air burst, since it does not result in the contamination of the ground with radioactive bomb residue. This type of burst results in blast, thermal and ionizing radiation injury (often combined in the same patient).

The only injurious agent peculiar to atomic warfare is ionizing radiation. With a high air burst these effects are due mainly to gamma rays, and they are no longer present after the first few seconds following the explosion. Although only about 15 per cent of the deaths resulting from this type of burst are likely to be due primarily to ionizing radiations, exposure to the latter may well complicate recovery from trauma.

Since there is a latent period of a number of days between the initial and later symptoms and signs of whole body radiation exposure, it does not constitute an emergency and can be treated after the initial period of the disaster has passed.

With the detonation of a contaminating burst (a surface, underwater or underground burst) the radii of damage from blast and thermal radiation are considerably less than with a high air burst. Two types of radiation may result from the radioactive fog (base surge) formed after an underwater burst—transit radiation and deposit or continuing radiation. The deposit radiation includes that resulting from inhaled or ingested radioactive material as well as that deposited on clothes or skin. Bomb residue contains material which would localize in bones if it entered the body, and much of it has a long radioactive and biological half-life. It would thus bombard the radiosensitive bone marrow for long periods.

Fortunately, the materials which would localize in bone are poorly absorbed from the gastrointestinal tract and lungs.

In general radiation injury to a person exposed to a contaminating burst should be reckoned primarily in terms of the penetrating gamma radiation to which he was exposed, rather than in terms of possible internal radiation from ingested or inhaled contaminants.

The principles of broad planning, careful triage, decentralization of medical aid, intelligent stockpiling, and the greatest good to the greatest number are to be stressed in medical defense planning.

The best appraisal of exposure and its degree of seriousness is, as it is with disease in general, an accurate clinical evaluation by the physician. The tempo of the disease is an important aid in evaluating severity of exposure. The use of the dosimeter in judging the fate of a given individual is, at least at present, of limited value.

THE purpose of this article is to present in a concise form aspects of atomic warfare that are of importance to the practicing physician who may find himself faced with the problem of caring for the victims of an atomic disaster. In the event of atomic attack on our cities the physician will be a key figure in providing health services to the victims, and it is therefore of the utmost importance that he be fully cognizant of the situation he may have to face shortly after the attack.

The number of dead and injured in the event of atomic attack would be overwhelming. For example, if this were to occur in a city with a population of a quarter of a million, 50,000 to 100,000 injured and 5,000 to 20,000 dead are not unreasonably high estimates. Thus, because of sheer numbers the casualties could not possibly receive what would normally be considered adequate care. In consequence of this, detailed advance planning is of the greatest importance. Such plans are dependent on a careful evaluation of the probable types of injuries, the relative numbers of each type, and the urgency of the need for treatment.

Any predictions of numbers of dead and injured can only be rough estimates at best, for the actual numbers would depend on the number of bombs used, the kind of bursts, the sizes of the bombs, the shape and topography of the targets, the weather, the time of day, the population density, etc. Most predictions have been for the air burst only, for this use of the weapon is believed to be the most destructive. However, the major effects of bursts of any

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The opinions set forth in this article are those of the writers and are not to be construed as official or reflecting the views of the U. S. Naval Radiological Defense Laboratory or the Navy Department.

type should be considered. A miss could conceivably convert what was intended to be an air burst into an underwater or surface burst.

KINDS OF ATOMIC DETONATIONS

Atomic detonations may be segregated into contaminating and non-contaminating. The only burst of non-contaminating type is the high air-burst, in which blast, heat, and ionizing radiation expend their energy over a wide area in the course of a few seconds. As the cloud ascends, all radioactive bomb residual is carried aloft and no significant* contamination of the ground with radioactive material occurs.[8] Essentially no ionizing radiation other than the immediate burst of gamma rays is encountered. It is as though a giant x-ray machine were suddenly turned on in the sky, and were left on for approximately one minute and then turned off. And just as one would not hesitate to enter an x-ray room and handle the patient immediately after the beam is turned off, so it is safe for rescue teams to enter the bombed area *immediately*.

A "contaminating" burst can be defined as any detonation in which the "fireball" comes in contact with the earth's surface. This results when the detonation occurs either on or below the surface of the earth, or at an altitude such that the "fireball" can touch the surface. The low air, the surface, the underground and the underwater burst are of the contaminating type. In general, the radii of damage for blast and thermal effects are decreased as compared with those of the air burst. The ground (or water) is actually contaminated with residual bomb products, both fissioned and unfissioned. Also, activity induced in the earth or water by neutrons liberated in the fission process may raise the general level of contamination.

With a burst of this type, then, the bombed area actually becomes radioactive, as though radium or other radioactive material had been spread over the area, and this radioactive material continues to emit ionizing radiation for long periods after the detonation. With a burst such as the underwater detonation, for example, it is likely that significant quantities of radioactive material can be carried well beyond the range of major blast or thermal damage.

The chief distinction between the contaminating and non-contaminating bursts lies in the presence or absence of residual radioactivity in the bombed area after the detonation. Blast, heat, and nuclear radiation may be present in varying degree in bursts of any type, but the magnitude of each effect in producing casualties will vary in accordance with the manner in which the weapon is used.

THE AIR BURST

The bursts of various types and the important phenomena associated with each have been reviewed. The effects of the high air burst will now be considered further. And while blast, heat, and ionizing radiation are treated separately, it is well to keep in mind that these phenomena rarely produce effects singly and, therefore, injuries generally would be multiple in nature.

Blast Effects

The effects of blast on man can be divided into two categories:

1. *Direct* effects resulting from interaction between the shock wave and the human body.

2. *Indirect* effects resulting either from objects set in motion by the blast striking the body, or from the body striking stationary objects.

Direct effects will be mentioned only to eliminate them from further consideration. There are essentially no circumstances during or following an atomic burst in which direct blast pressure could injure a person who would not be killed "many times over" by other effects.

Indirect blast injuries are mechanical injuries and are similar to those produced by falls, by blows with blunt instruments, or by automobile accidents. They consist of contusions, lacerations, simple and compound fractures, internal injuries, penetrating wounds, crushing injuries, etc. Injuries from flying glass would be extremely common. In the Japanese disasters mechanical injuries among survivors were in general of a minor nature; the absence of major trauma among survivors is ascribed to the fact that victims so afflicted could not escape the conflagration which developed in the first few hours after the burst.[12] In cities of more fireproof construction, or under improved conditions of rescue, the number of survivors with major traumatic injuries might well be much larger than it was in Japan.

The kind of mechanical injury referred to is, of course, not peculiar to the bomb. But it must be remembered that there might be *thousands* of victims with injury of this type for whom treatment would be needed almost simultaneously. There would be neither time nor facilities to care for all of them adequately.

Thermal Effects

The thermal radiation from the exploding bomb can cause injury in two ways:

1. The radiant heat may act directly on exposed personnel and produce *primary burns* or *flash burns*. This kind of injury would happen only to people who were in the open or near a window.

2. The radiant heat can char structures, clothing and other combustibles in the affected areas, and those burning objects may themselves inflict burns. Such burns are termed "*secondary*" burns.

Actually, radiant heat probably would contribute much less to the igniting of materials than would overturned stoves, electrical "shorts," etc. At any rate, in the first few hours following the burst, a widespread conflagration would kill potential survivors trapped in the wreckage or otherwise unable to leave the scene.

The extreme rapidity with which the thermal radiation is delivered and the relatively poor heat

* There could be some ground contamination resulting chiefly from a "fall-out"; but the levels of activity would be very low and would constitute a minor hazard compared to the gravity of the over-all situation.

conductivity of the skin results in burns that are in general superficial and painful, but which may be deep in victims near ground zero.* "Shadow effects" are common; a man be shielded by buildings, clothes, or even by body contours.[12] Radiant energy burns generally are on one side of the body only. Patterned clothing may permit burns beneath dark-colored areas while the skin beneath the light areas is not burned.

Burns present no new problem, but it must be recognized that they are large open wounds and that shock and infection are a serious threat. Flash burns are not uncommon in industry, and certainly the treatment of burns from flaming structures is in every physician's experience. The well-known factors of the location, the degree and the body area involved enter into the appraisal of the severity of the burn.

Effects of Ionizing Radiation

The only injury peculiar to atomic warfare is that caused by ionizing radiation. However, in the event of an airburst ionizing radiation would not be the chief cause of mortality. Only 15 per cent of the Japanese fatalities are attributed primarily to ionizing radiation.[12] But if measures are taken to prevent thermal and blast injury, ionizing radiation would assume much greater importance because it is more difficult to shield against.

Radiation injuries resulting from a high air burst are chiefly the result of the gamma rays which are liberated during the first few seconds.† As was stated, these penetrating gamma rays are similar in all respects to high-energy x-rays. The biological effects of such rays can be duplicated in the laboratory by the use of either high energy x-ray machines or by use of gamma ray sources.

The sudden burst of gamma rays from an air burst may be important from two aspects:

1. Large doses of the rays will produce the clinical picture of acute radiation injury,[7] or this picture as it may be modified by partial shielding of the body.

2. With smaller doses, although the complete clinical picture of acute radiation injury may not be evident, exposed persons may become debilitated and particularly susceptible to infection.[13] This complicating factor may interfere with healing of burns and traumatic injuries.

The clinical picture of acute radiation injury can be characterized as follows:[10]

Following an exposure to a large dose (300 r to 500 r) anorexia, nausea, vomiting, malaise, fever and thirst may appear in the first few hours. These symptoms subside and are followed by a period of variable length (a few days to a few weeks) in which the patient is apparently well. During this period leukopenia, thrombopenia, and disappearance of reticulocytes become evident. A decrease in lymphocytes appears early and the granulocyte changes follow. Anemia is slow in developing.

The latent period usually ends with the onset of epilation, usually of the head, and often of the armpits and pubes. This is reversible. Anorexia and malaise return, as does a stepwise-rising fever. Pharyngitis and oropharyngeal ulcerations (agranulocytic angina) appear; then bleeding tendencies—petechiae, bloody diarrhea, nose bleeds, purpuric spots, etc. This may be followed by the development of enteritis, hemorrhagic lobular pneumonia and other infections that may result in death. Occasionally, a more prolonged course characterized by debilitation and emaciation may precede death.

In patients who recover, the signs and symptoms of the disease disappear approximately in the following order: pharyngitis, diarrhea, petechiae, fever, and oropharyngeal lesions. Recovery is associated with an increased leukocyte count in the peripheral blood. However, a patient in whom the leukocyte count is returning to normal may die. Anemia in survivors extends into the period of convalescence.

The pathogenesis of this disease insofar as it is understood at present, is as follows: There are three tissues affected in the main, the bone marrow, the lymphoid tissue, and the gastrointestinal tract. The disease in its terminal stage is not unlike advanced aplastic anemia. With large doses of radiation the result is aplasia of the bone marrow. This results in the blood picture which was described. The low leukocyte count coupled with disturbances of other immunizing mechanisms contributes to a lowered resistance to infection, which in turn permits development of oral, gastrointestinal and pulmonary lesions. There is an absence of cellular tissue reaction around these infectious lesions.

The decreased platelet count is probably an important cause of the hemorrhagic tendency. Also involved possibly are an increase in circulating heparin-like substances in the blood, and an increased capillary fragility. The lack of erythrocyte production and the bleeding tendencies are mainly responsible for the anemia. Infection may also be a contributing factor to the anemia. Depression of the erythroid elements of the bone marrow is pronounced. This is reflected in the reduced uptake of administered radioactive iron into the erythrocytes following total body radiation.

The diarrhea, which is often sanguineous, has been explained on the basis of edema of the bowel, denuding of the mucosa secondary to infection, and hemorrhage.

A most important characteristic of acute radiation injury is the latent period: A severely exposed person may have no serious signs of illness for a number of days. It should be recognized, then, that acute radiation injury does not constitute an emergency and can be treated after the trying initial period of disaster is over.

The dose of gamma radiation necessary to produce death or serious illness depends on several bio-

* The point on the ground nearest the center of detonation.

† The effective range of neutrons liberated during the fission process does not extend beyond the range of total destruction. However, they may assume greater importance in that, if shielding were available to protect adequately against heat, blast, and even gamma rays, neutrons might still be lethal.

logical and physical factors. The dose necessary to kill approximately 50 per cent of a group of exposed human beings† is usually taken to be 400 r, although a few may die after doses as low as 200 r and a few may survive doses as high as 600 r. Hence it is seen that a large individual variation in susceptibility exists. In addition, the previous condition of the exposed person is important in determining the response and prognosis. A sick person is more likely to have serious effects from a given dose of radiation than is a well one. Subclinical or low-grade infections that in themselves would not be lethal may, in conjunction with a usually sublethal exposure to radiation, cause death.[3]

The existence of partial body shielding may be important in establishing the prognosis of a patient, and victims should be questioned about possible partial as well as total shielding. To take an extreme example, if 10,000 r were directed to a small region of the body, i.e., the hand, the victim would not die of "acute radiation injury." But if 400 r were delivered to the whole body about 50 per cent of victims would die. If the abdomen were completely protected with lead,‡ the dose necessary to kill 50 per cent of exposed persons would be of the order of 1,200 r. If everything but the abdomen were protected and the abdomen irradiated, the LD_{50} dose would be about 600 r. The abdomen-shielded persons would probably have a syndrome different from that of those who received whole body irradiation, and the time of death of the abdomen-irradiated persons would probably be earlier than that of the abdomen-shielded. Head irradiation alone probably would produce death at doses of the order of 1,200 r. Obviously, these figures were derived by extrapolation from animal experiments[2] and can be regarded only as rough approximations.

It was stated earlier that the energy of the gamma rays is very great.[8] This high energy is of importance in that it can produce essentially "whole body" radiation in man. This may be clarified if it is pointed out that if small animals such as the rat or mouse are irradiated with 250 KVP x-rays, the energy absorbed at different depths of the animal will be sensibly the same. However, if a large animal the size of a man is irradiated with x-rays of the same energy, the irradiation of the tissues farthest from the beam would be decreased by a factor of approximately ten. If higher energy or more penetrating radiations are used, the dose received throughout an animal tends to be more uniform.

The total dose of radiation that may be received from a high air burst is delivered over a few seconds. There is no time for recovery during irradiation and the effects are maximal. If the total dose is given over several days, for example, as opposed to a few seconds or minutes, the dose necessary to produce serious damage is larger. If intermittent or repeated exposure is experienced, the dose necessary to produce serious damage is also increased. This, again, is because recovery is permitted during irradiation.

Numbers of Injured

The effects of blast, thermal radiation, and nuclear radiation have been considered separately. It is of importance to consider these injuries collectively, to gauge the relative numbers of each kind and to consider where they occur with respect to ground zero.

It is stated frequently that (assuming detonation of the nominal or 20 kiloton bomb) of the people present in the zone extending from ground zero to one-half mile from ground zero, 90 per cent or more would be dead or injured, and that in the second zone extending from one-half mile to one mile, some 80 per cent would be dead or injured. Such a representation, however, is in a sense misleading, for the more remote the zone from ground zero, the greater the population in it because it is of greater area. When 90 per cent or more of the population of the innermost zone are dead or injured, this is a large percentage of a relatively small number of people. Also, the physician would be primarily concerned with the injured survivors, and from this standpoint it is necessary to consider that most of the people in the innermost zones would be killed. Of more importance to the rescuer is a consideration of the probable number of *survivors* in each zone and how many of them are likely to be injured.

Exact figures are not available but it is probable that most of the injured would be found in the zone extending from one mile to a mile and a half from the center of the blast. Considering again that radiation is falling off rapidly at one mile while heat and indirect blast effects are still important at two miles, it is obvious that in the zone where most injuries are likely to occur radiation is not a significant factor. In other words, most of the injured there would have blast injuries or burn injuries or both.

However, it should be stated also that a sizable percentage of survivors needing treatment would be in the zone extending from one-half mile to one mile from ground zero, where gamma rays are still effective. Hence radiation damage can be expected, not only as a primary entity but as a serious complicating factor. The importance of radiation should not be over-emphasized—or discounted.

It should be pointed out again that with modern structures providing protection against heat and blast, and with improved rescue techniques, the chance of survival closer to the bomb is greater and hence the probability of radiation injuries is increased. It should also be reemphasized that only the burned and traumatized victims will need emergency treatment, for lesions and accompanying shock; acute radiation injury, or complicating radiation dosage, does not constitute an emergency.

As to the numbers of casualties, totals are dependent on the size of bomb, type of bomb, number of

† A species difference exists;[9] the LD_{50} for rabbits is about 750 r; for rats, about 650 r; for goats, about 350 r; for dogs, about 300 r. Since most animals that die after acute total-body irradiation do so in 30 days or less, the period of observation for lethality is taken as 30 days, e.g., the $LD_{50/30}$ days is determined. Many severely exposed human beings, however, die between the 30th and 60th days after exposure.

‡ The weight of material required makes it appear at present that a partial body "armor" against bomb radiations is impractical.

bombs used, density of population, etc. But a figure of 50,000 persons who need treatment in a city of 250,000 or more is conservative; 75,000 or 100,000 is not unreasonable. Furthermore it must be remembered that treatment for all *simultaneously* would be required. Relative numbers of casualties can be gained from the following hypothetical breakdown of injuries:[12] Wounds, 70 per cent; burns, 65 to 85 per cent; radiation injury, more than 30 per cent.

Perhaps of more practical value would be information on the expected diagnosis and outcome per 100 casualties. This could be represented as follows:[11] Wounds (no burns), 60; burns (with or without wounds), 40; radiation injury, any degree, 30; died (all causes), 25; died of burns, with or without other injuries, 19; died of wounds, 6.

THE CONTAMINATING BURST

The radius of damage from blast or heat with a burst of the contaminating type would be, in general, less than that of the high air burst. With the subsurface burst, effects of radiant heat might be entirely absent. With an underwater burst off shore, blast may be no problem at all to shore establishments. With the underground burst, it is not unlikely that an earthquake-like phenomenon might cause destruction at a considerable distance.

As with the high air burst, direct blast effects (in air) would be of no practical concern. Indirect blast injuries and burns, if they are present, would not differ qualitatively from those of the high air burst. There might be few or no flash burns and relatively larger numbers of flame burns.

As to radiation encountered with the contaminating burst, some elaboration is necessary. For example, in the underwater burst, as the large mass of water thrown into the air by the detonation falls to the surface, a highly radioactive fog or base-surge forms, which rolls over the bombed area and then ascends into the sky.

Radiation delivered from the base-surge can be divided into two types, transit radiation and deposit or continuing radiation. The transit radiation is delivered as the base-surge rolls over the area and ascends into the sky. Again it is as though a giant x-ray machine had been slowly drawn over the area and then pulled up into the sky out of range. Radiation of this type is delivered to the bombed area over a matter of minutes. It then disappears.

The transit radiation of medical importance, then, is delivered over a short period of time, as with the air burst, and is composed of gamma or penetrating rays like x-rays. Like the high air burst, it can produce total body radiation resulting in acute radiation injury. But as the base-surge rolls over the area, it rains or deposits radioactive materials on objects and personnel below. It is as though a large quantity of radium or other radioactive material had been spread over the bombed area.

The deposit radiation can get on the clothes and on the skin. Here again the x-ray analogy may be used. But here the "x-ray machine'" has not been lifted out of range; it remains on the clothes or on the skin. Still, penetrating gamma rays are given off; still, whole body radiation resulting in acute radiation injury may be produced.

And suppose a person even ingests or inhales the base-surge? Here he has taken numerous "small x-ray machines" or radioactive isotopes into the body; they continue to give off penetrating radiation, the entire body can be irradiated, and acute radiation injury may occur. Again, if large amounts of radioactive fog or mist from the bomb are deposited on the clothes or skin, or even enter the body, acute radiation injury may result.

The penetrating gamma rays are the chief or "controlling" hazard to personnel contaminated shortly after the detonation. But other hazards result from the deposition of radioactive material from the bomb, and in order to describe and evaluate their role it is necessary first to elaborate further on the composition of the radioactive bomb residue.

In addition to gamma emitters, the bomb residue also contains beta-emitting fission products. The emitted beta rays are termed non-penetrating, since fairly energetic beta rays penetrate only a centimeter or less in tissue. If present on or near the skin in large quantities, these rays can produce "beta burns." If beta emitters are inhaled or ingested, the lungs or the gastrointestinal tract can become irradiated.

Unfissioned bomb residue (plutonium or uranium) emits alpha rays. If small quantities of this material gain access to the bones, serious chronic effects may result. A well-known example of this type of injury is that of the watch-dial painters. These people, while pointing their brushes with their lips, ingested enough radium and mesothorium (also alpha emitters) over a long period of time to localize in the bones and cause death after several years, from anemia, infection or osteogenic sarcoma. Certain long-lived beta-emitters found in the bomb residue also localize in the bones and are capable of causing this type of damage. All such long-lived elements (either alpha or beta emitters) can be called collectively the "bone seekers" and can give rise to an "internal radiation" problem. In general, bone seekers are very poorly absorbed from the lungs and gastrointestinal tract, and relatively large quantities must be inhaled or ingested before dangerous amounts gain access to the bones.

To evaluate the hazards from these sources it is necessary to consider the relative amounts of the different types of radiation associated with a given quantity of bomb residue. Initially (soon after the detonation) the amount of gamma and short-lived beta emitters associated with any significant quantity of "bone-seeker" is very large; relatively, the gamma radiation is the overwhelming hazard. The gamma-emitters in general, however, have extremely short half-lives; as time goes on after the burst, the gamma hazard becomes very much reduced and, relatively, the "bone seeker" or "internal radiation hazard" becomes of greater importance.

The important conclusions from these considerations are as follows: Radiation injury to a person

exposed to contamination at the time of an atomic detonation should be reckoned primarily in terms of the penetrating gamma radiation to which the person was exposed. Associated acute beta radiation to the skin or to the lungs or gastrointestinal tract can occur, but, in general, cases of severe exposure of this nature will not be a serious problem. If a victim is exposed to the base-surge and ingests or inhales "bone seekers" in dangerous quantity, he is likely to have received a sufficiently large dose of gamma radiation to result in death before the "bone seekers" can become dangerous.

This does not mean that contamination should not be removed from the skin, for no irradiation should be taken lightly. But the surviving patient should be assured that even though he may have some contamination on his skin as he emerges from the bombed area, if he survives the first few weeks (acute radiation illness period) he is in all probability not doomed to the chronic disease observed in the watch dial painters.

It should be emphasized that the above considerations apply only to victims emerging from the bombed area—that is, the patients who will be seen immediately after the burst. It does not apply to clean-up or reoccupation operations at a later date when the rapidly decaying gamma emitters have essentially disappeared. Here long-lived bone-seekers can be a serious problem. In general, however, such a situation would be encountered late after the bomb detonation and operations would be organized under radiological specialists. The responsibility for radiological safety will not, in general, fall to the practicing physician.

It was stated previously that gamma radiation decreases in amount very rapidly immediately after the burst. An idea of the rapidity of the decay can be obtained from the statement that if a man is trapped in the bombed area and received 100 r over the first hour, if he remains in the area for days or even weeks he will receive a total of only about 120 r.[14] Hence, if a man emerges from the bombed area and has significant amounts of radioactive contamination on him when observed medically, he should be treated as a potential radiation injury casualty. The chances are great that if he is significantly contaminated when he emerges, he has received a large dose of radiation before he emerged.

MEDICAL DEFENSE PLANNING

A resume of the physical and medical effects of atomic bomb detonations has been presented. Consideration must now be given to the means of handling the situation from the medical point of view. The bomb has exploded; the damage has been done; now what is to be done? The task is an overwhelming one. It is of such magnitude that it cannot be considered in ordinary frames of reference. Defense planning on a local level alone would be disastrous. Regional and nationwide planning are mandatory if effective countermeasures are to be developed.

The guiding principle of the defense plan must be the greatest good to the greatest number. This must be emphasized again and again. Selfish motives and self-interest must give way to unified action according to plan.

Medical defense planning is a large subject and it is obviously not possible to cover it adequately in a relatively short article. It will, therefore, be possible to cover only the principal aims of a medical defense plan and how they can be accomplished.

After an air burst has occurred in an urban area, for example, a stream of injured would begin to pour out of the bombed area, leaving behind many seriously injured who could not move out under their own power. Rescue teams would enter the stricken area to guide the stream of victims to medical aid stations and to evacuate the seriously injured. It is natural to inquire, then, into the question of when and where the injured would be cared for. It is obvious that the patient and the physician and his supplies and facilities must be brought together in time and place. Is the patient taken to the treatment center or the treatment center to the patient? In other words, just how much can be mobilized effectively and taken to the patient, and, conversely, how far can the patient be transported? In short, the patient is brought as far as his condition will permit and the availability of facilities for his care requires. Transportation to a point where safety from burning and falling debris is assured is axiomatic.

In order to decide, then, on the kind of treatment facilities needed and where they should be available, the casualties must be analyzed according to severity of injury. Persons mortally wounded would, of necessity, be transported only short distances if at all. That would include persons in shock or impending shock, those with respiratory embarrassment and those with hemorrhage. Their care would be provided for by mobile units on the spot or in casualty stations at the perimeter of the disaster area. The seriously injured who can be transported would be cared for in evacuation hospitals to the rear of the bombed area. It would be necessary to evacuate patients to neighboring cities for care. Persons with minor injuries would be attended to in the casualty stations. If at all possible the latter should be treated far to the rear of the bombed area, thus reserving the close-in facilities for the patients who could not be moved.

It follows that a very important consideration in medical disaster planning is adequate triage or sorting of patients. This would be done at the forward stations. Decentralization of medical aid with large numbers of smaller mobile units and casualty stations would be desirable. Patients would not have to travel so far, and destruction of large centralized facilities would be minimized by this means.

Because of the enormous supplies of plasma, plasma substitutes, bandages, splints, essential drugs, etc., which would be needed, adequate care of victims would depend on stockpiling well in advance of expected attack. Neighboring areas must plan to cooperate by sending physicians and supplies to the bombed area and by receiving evacuated patients.

Rescue teams and personnel of the treatment units

would not, in all likelihood, find the victims of an atomic disaster easy to handle.[13] They probably would be stunned and bewildered. Also they might be anxious and grief-stricken, or even hostile. Hostility might reach the point of physical violence toward the rescuer at what might be interpreted as neglect of members of a victim's family in favor of other victims. It is, of course, obvious that medical supplies would have to be conserved. Vitally needed supplies and equipment ought not be depleted by ill-considered use on persons only slightly injured, or on those beyond medical aid.

In atomic attack the psychological factors would be increased because the populace would be unaware of the nature of the attack. In view of the psychological aspects of the problem, rescue personnel would require police power and weapons to enforce it. They would then also be empowered to prevent unauthorized use of vehicles in the disaster area and thus prevent interference with rescue operations. Pillage is, of course, a usual concomitant of disaster, and the measures mentioned would help prevent it.

Indoctrination programs should be instituted to reduce the psychological problems the rescuer probably would encounter. In the process of the indoctrination to prevent anxiety, consideration should be given to some of the misconceptions regarding the effects of irradiation. For example, contrary to the belief of some persons, acute radiation injury is not a communicable disease, nor does it cause the patient to be radioactive. Many people believe that it is possible for an object or person contaminated with radioactive material to render objects or persons in the immediate vicinity radioactive without actual contact. This is, of course, false, for contamination can only be the result of actual transfer of radioactive material from one object to another.

Cancer is thought to be an occasional sequel to periodic radiation exposure. There are little or no data to indicate an increased incidence of cancer among survivors of a single acute exposure, although it appears likely that the incidence of leukemia will be higher among the Japanese survivors than in the population as a whole.[11] Cataracts of varying severity have appeared in Japanese survivors; but the incidence to date is low. Sterility was rare and transient, and the incidence of abnormal offspring did not increase.

Radiation exposure is commonly thought to result in impotence. This is, of course, false. Such a condition can result from emotional stress in predisposed persons, and such stress is quite possible in the bombed population. However, the incidence of this condition among Japanese survivors was very low.

Education of the public, and proper indoctrination of rescue teams, will go far to diminish the psychological stress and the resulting deleterious effects of it following an atomic burst.

THE INDIVIDUAL CASUALTY

Diagnosis

It has been emphasized that blast and burn casualties will constitute the main problem. Careful evaluation of the burned or otherwise injured patient will be necessary, but the diagnostic problems are not new. However, since acute radiation injury has not been observed by many American physicians, and since its manifestations are, for the most part, delayed, it will present a diagnostic and prognostic problem.[7, 8] It is of value to decide what criteria are available to determine what persons have been irradiated, and to what degree.

Some information on dosage received can be gleaned from (1) the dosimeter reading, if available, and (2) the position of the person relative to the site of detonation. Dosimeters either on or in the vicinity of the individual will indicate the order of magnitude of dosage received. Knowledge of the position, if the kilotonnage of the bomb is known, will also permit estimation of dosage—a person in the open, 4,200 feet from the epicenter of a 20-kiloton bomb, would have received about 400 r, while a person at 5,200 feet would have received about 100 r. The size of the bomb can be approximated soon after the blast, and the distance-dose relationship should be available early.

Such estimations of dosage are excellent as a basis for over-all planning. As an accurate index of the probable fate of an *individual*, however, such estimations at present are of limited value. Dosimeters indicate the dose received by the instrument, which may be only a rough approximation of the effective dose received by the person in question. The position of an individual is obviously but a rough index of dosage received. Neither the dosimeter reading nor position take adequate account of the energy of the radiation, nor the degree of partial or total body-shielding of the individual; and, most important, the extreme degree of variation in response of individuals. Hence, neither the dosimeter readings nor position data should be used *by themselves* as the final index for triage, therapy, or prognosis. That is, there may be a vast difference between the presumptive diagnosis resulting from physical data and the diagnosis resulting from an over-all clinical evaluation of the patient's status.

The best appraisal of exposure, and degree of exposure is, as with any disease, an accurate clinical evaluation by the physician. A thorough evaluation can result only from a history (which includes any physical estimates of dose), a physical examination, and pertinent laboratory data. Symptoms suggestive of radiation injury include vomiting on the day of the bombing, oropharyngeal lesions, and hemorrhagic manifestations other than cutaneous purpura. Specific symptoms include epilation and purpura.[11] The presence or absence of the symptoms indicated previously (anorexia, malaise, diarrhea, melena, etc.) are of considerable value in appraising the status of a patient.

The degree of exposure can be estimated fairly accurately by the tempo of the disease. For instance, if vomiting on the day of the bombing proceeds without remission to other symptoms of the disease, exposure probably was severe and the prognosis is grave. If vomiting on the day of the bombing is followed by a remission, or if vomiting is absent

entirely, the probability of severe exposure is less and recovery is likely.

The clinical laboratory can provide data of inestimable value in early diagnosis and prognosis. Pronounced leukopenia is indicative of severe exposure, and a total leukocyte count of below 2,000 per cubic mm. of blood in the first week is indicative of very severe prognosis. A total lymphocyte count of less than 800 per cu. mm. two days after exposure is presumptive evidence of severe radiation exposure.[11] A significantly lowered absolute lymphocyte count within 24 hours is quite suggestive of such exposure.

Platelet counts remain stable for several days following exposure; however, a greatly decreased platelet count one week after exposure is indicative of severe overexposure. Anemia appears late, as much as two to three weeks after exposure; hence the erythrocyte count is not a good early index of damage. However, an increase in reticulocytes any time after exposure is a very good prognostic sign.

Treatment

It remains to examine what can be done for the patient with acute radiation injury. The treatment of this disease is at this time entirely symptomatic and supportive, and physicians in general have had no clinical experience with acute radiation injury. Nevertheless, intelligent care, even if only of a supportive nature, would salvage a great number who might otherwise die.

The severely irradiated patient should be put at complete bed rest as soon as possible after exposure. It has been shown with laboratory animals that repeated vigorous exercise considerably increases mortality.[9]

The use of antibiotics in the irradiated patient would probably be of definite value. Antibiotic therapy should probably await a clear-cut clinical indication for it. However, optimum dose schedules for man must await further clinical experience. Large doses probably would be needed to offset the lack of immune responses of the irradiated subject.

The value of transfusions in radiation injury is in doubt at this time. However, should transfusions be used they probably would not need be started until anemia was present, generally two weeks or more after exposure.

Adequate fluids and salts should be given to replace losses due to vomiting and diarrhea. The oral or rectal route should be used if possible; needle punctures would be hazardous because of the bleeding tendencies and the decreased resistance to infection of the irradiated patient.

The bleeding tendencies might be treated with protamine or toluidine blue. These are believed to combine with the heparin-like substances said to be present in the blood in excess concentration. Neither this mechanism of the hemorrhage nor the efficacy of this type of treatment has been established in man.

Vitamins C, P, rutin and various flavinoids have been suggested as being of some value in preventing capillary fragility. These are of doubtful value in preventing the hemorrhagic effects in the irradiated patient.

Oxygen may be efficacious in alleviating the tissue anoxia, which may be present in radiation injury.

A liquid diet should be used early. Later, a smooth diet should be given, since injured gastrointestinal tract mucosa will not tolerate even mild trauma.

Little benefit may be expected from iron supplements and folic acid. Several prophylactic agents such as cysteine, glutathione, and substances producing histotoxic anoxia (cyanide, thiouracil, etc.) have been found to be of value in animals if administered prior to irradiation. No such drugs have been tried for whole body irradiation in man, and at present there is no prophylactic agent of practical value for use in human beings.

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NOTE: *The California Civil Defense Authority created a State Radiological Safety Evaluation Board after this article was accepted for publication. This board in turn has created a series of Regional and Area Evalution Boards which are now in process of organization and rehearsal. These boards will be composed of radiologists and other persons familiar with radiation hazards, and will work in cooperation with local fire and police departments in the event of a bomb strike. Their work will be integrated with the Radiological Defense Division of the State Civil Defense Program.*

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The Rh Factor in Rural Practice

Responsibility of the General Practitioner

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SUMMARY

As the incidence of erythroblastosis fetalis is as high in rural as in urban areas, it behooves physicians in rural areas to anticipate the disease, to make special antepartum studies to determine the Rh status of obstetrical patients, and to be prepared to treat the affected baby if the aid of a specialist and special facilities are not obtainable.

Exchange transfusions have been carried out, by means described, in a small rural hospital.

ERYTHROBLASTOSIS fetalis, or hemolytic disease of the newborn due to Rh incompatibility between mother and fetus, is not limited to large medical centers. The emergency confronts physicians in rural areas.*

The incidence of erythroblastosis is usually given as one in 200 pregnancies,[8] and an affected baby has less than a 50 per cent chance to survive without treatment.

The purpose of this presentation is to review fundamentals which have practical clinical application to the management of Rh problems in rural practice, and to outline a plan for management which has been successfully used in a rural area.

GENETICS AND IMMUNOLOGY

All human blood may be divided into four main groups according to the presence, or absence, in the erythrocyte of one or both of the A and B agglutinogens. These are not the only antigenic substances which may be present in the erythrocytes in human blood, and among the others is the antigen called the Rh factor.

The Rh factor is inherited. It is a Mendelian dominant characteristic. The fetus will be Rh-positive if either parent contributes the dominant Rh-positive gene. If the same factor is in both chromosomes the person is homozygous; if otherwise, heterozygous. If a homozygous Rh-positive male marries an Rh-negative female, all the children will be Rh-positive. If he is heterozygous, half of the children will be Rh-positive and half of them Rh-negative.

In 85 per cent of persons (95 per cent of Negroes) the erythrocytes contain the Rh factor. These persons are Rh-positive. Conversely, 15 per cent do not have the factor and are called Rh-negative. It follows that exposure of an Rh-negative person to the antigenic Rh factor in erythrocytes of Rh-positive persons might stimulate production of Rh-antibody substances in the Rh-negative person. If this occurs, the Rh-negative person is said to be sensitized or iso-immunized.

There are two ways by which an Rh-negative female becomes sensitized: By receiving injections of Rh-positive blood, and by repeated pregnancies bearing an Rh-positive fetus. Pregnancy is a less potent immunizing factor than is injection of Rh-positive blood. There is in general a 1:30 chance that an Rh-negative woman will become sensitized.[7] There is only a 1:1,000 chance for immunization by pregnancy alone in the primipara but for the second and third pregnancies the chances are 1:40, and they increase to 1:12 for the fifth and sixth pregnancies. In contrast, antibodies develop in about 50 per cent of Rh-negative women with a history of blood transfusion. If this happens before the first pregnancy, it is likely the first child will have severe erythroblastosis.

ESSENTIAL LABORATORY TESTS

When there are no clinical laboratory services available, tests for the Rh factor and erythroblastosis can be reduced to two: Typing for the Rh factor, and the Coombs test. Rh typing identifies the Rh-negative mothers, and the Coombs test on cord blood of the infant is a diagnostic test for erythroblastosis. These inexpensive procedures physicians can do personally, preferably after observing them done in experienced hands.

While tests for Rh antibodies in the maternal circulation are desirable when laboratory help is available, they are not suitable as an office procedure.

Typing for the Rh Factor: One drop of commercial† anti-Rh serum is added to two drops of fresh blood being tested. These are mixed on the warm glass plate of an Rh view box and the plate tilted back and forth slowly. If clumping occurs, it is complete in one to three minutes. Agglutination means the blood is Rh-positive, no agglutination that it is Rh-negative.

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* In California in 1949 there were 157 recorded infant deaths attributed to erythroblastosis and only nine to syphilis. In 1949 the incidence of infant deaths due to erythroblastosis was the same in rural areas as in urban areas of the state.

† Materials used are available from American Hospital Supply, Lederle, Ortho Pharmaceutical, and others.

The Coombs Test: Two drops of Coombs' anti-human-globulin reagent (Ortho) is added to two drops of a 2 per cent saline solution suspension of washed erythrocytes being tested. These are mixed gently in a small test tube. If the cells are heavily coated with blocking antibodies, agglutination will occur almost immediately. If weakly coated, incubation at room temperature for ten minutes followed by slow centrifugation will cause agglutination. A positive result in the Coombs test means erythroblastosis; a negative result may not rule it out.

Although the significance of Rh antibody determination will be discussed, the techniques will not be described since they require a well equipped laboratory. In general, laboratory determinations made before delivery cannot be accurately correlated with the certainty of occurrence of erythroblastosis in the fetus or with the severity of the condition if it does develop.[6] Mothers of most severely affected infants usually have high antibody titres, yet many in whom sensitization is demonstrated deliver an unaffected baby.

There are two types of Rh antibodies. One is the agglutinin, or complete antibody, which in its specific reaction with the Rh-positive erythrocytes causes complete hemolysis of the cell. It is sometimes designated the "saline fraction," as it is demonstrated in a saline medium. The other, the blocking antibody, or albumin fraction, is sometimes called the incomplete antibody since it attaches to, or coats, the surface of the fetal erythrocyte without causing hemolysis. It can be activated to complete the hemolytic reaction by addition of an X-protein factor (conglutinin) found in human plasma or bovine albumin. The blocking antibody is thought by some investigators to protect the fetal erythrocyte it coats, since it appears to block direct hemolytic action of the circulating agglutinin.

MANAGEMENT OF OBSTETRICAL RH PROBLEMS IN RURAL AREAS

The suggested outline for management of obstetrical Rh problems in rural areas is based upon three possible situations depending on the presence or absence of laboratory and specialty help:

1. Management when neither laboratory nor specialty help is available:

(a) On the first visit a careful, complete obstetrical and transfusion history should be obtained.

(b) Rh typing of each obstetrical patient should be carried out. (Fifteen per cent will be Rh-negative.)

(c) The Coombs test should be applied to every infant born to an Rh-negative mother.

(d) If the Coombs test result is positive and criteria for a diagnosis of erythroblastosis are present, a blood transfusion for the infant must be considered. If possible, arrangements should be made for an interested pediatrician to treat the baby. Expense and time involved in bringing a specialist to the baby are often prohibitive. The same is true of transfer of the baby to a medical center, plus the fact that travel is hazardous for the baby. Another alternative would be to send the mother to a center to await delivery. This is usually impossible. Faced with these problems, the physician is likely to be left with a choice of attempting the transfusion or standing helplessly by with the infant's life at stake.

2. Management when laboratory but no specialty services are available:

(a) A careful obstetrical and transfusion history.

(b) All obstetrical patients should be referred to the laboratory for Rh typing and routine determinations of blood factors. Mailing containers may be used for sending specimens of blood to the laboratory.

(c) If the blood is Rh-negative, antibody determinations should be carried out. The presence of antibodies early in pregnancy usually indicates sensitization with carry-over from previous exposure to the Rh antigen.

(d) Titration tests should be repeated at the seventh month. If results are negative, no more tests need be done. If positive, titrations should be determined again at the eighth month. A rise in titre may be significant.

(e) The cord blood of infants delivered of Rh-negative mothers should be subjected to the Coombs test.

(f) Arrangements should be made for transfusion if it appears the procedure will be necessary.

3. Management when laboratory and specialty help are both available:

(a) Preliminary tests as previously outlined.

(b) Consultation with appropriate specialists to form a team prepared to carry out indicated therapeutic measures. (Rarely will this be possible in rural areas.)

It is not advisable in rural practice to induce labor early, or to carry out cesarean section in an attempt to minimize damage to the baby. Disadvantages of prematurity offset any advantage gained, especially when facilities for the premature are not ideal.

Efforts to prevent maternal antibody formation and to block action of the antibodies in the fetus have not been very successful. Some of the many agents tried are methionine, vitamin K, liver extract, progesterone, the hapten of Carter, cortisone and adrenocorticotropic hormone (ACTH). The latter three can possibly do harm and should not be used in rural practice.

SIGNS OF ERYTHROBLASTOSIS IN THE INFANT

The pathogenesis of erythroblastosis has already been touched upon. In some manner erythrocytes of the fetus reach the maternal circulation. If the mother is Rh-negative, she may be stimulated to produce Rh antibodies which pass easily into the fetal circulation where they may cause hemolysis of fetal erythrocytes. The fate of the fetus, depending on the degree of hemolysis, varies from intra-uterine death to being born alive only to have hemolytic

crisis follow. The demand to produce erythroblasts may be so great that immature nucleated cells (erythroblasts) appear in the circulation of the fetus. The liver, spleen, and other organs may assume erythropoietic functions. This leads to the greatly enlarged liver and spleen often observed in babies with erythroblastosis.

Clinically, the symptoms may be of one of three forms of the disease:

1. *Hydrops fetalis* is the most severe form. The baby has severe generalized edema, dome-like abdomen and huge liver and spleen. There is no effective treatment. The baby is usually born a month prematurely and, if born alive, soon dies.

2. *Icterus neonatorum* is the form in which the infant, at birth or soon after, has severe hemolytic anemia and jaundice. There may or may not be hepatomegaly and splenomegaly. The mortality rate for babies with disease of this type (untreated) is more than 50 per cent. Exchange transfusion has reduced this figure to as low as 2 per cent.[8]

3. *The anemic type* is the mildest form. The problem is that of severe anemia which may develop rapidly or be slowly progressive over a period of weeks. The mortality rate if the baby is not treated is around 25 per cent. Perhaps all babies with this form of the disease could be saved by adequate care.

Laboratory determinations supporting a diagnosis of erythroblastosis may be divided into (1) those present in the prenatal period, such as maternal antibodies and x-ray films in which the fetus is observed in a Buddha-like position with a halo shadow about the scalp due to edema; and (2) postnatal data, including a positive result of the Coombs test, less than 16 grams of hemoglobin per 100 cc. of cord blood, a ratio of more than five immature nucleated erythrocytes per 100 leukocytes, and bilirubin content of over 3.0 mg. per 100 cc. of cord blood.

MANAGEMENT OF ERYTHROBLASTOTIC INFANTS

In the management of an erythroblastotic infant, at birth the cord should be clamped long and the cord blood collected for a Coombs test, for hemoglobin determination and for cell study. The baby should be placed in an incubator with oxygen flow on. Since many erythroblastotic infants appear normal at birth but within a few hours have severe anemia and jaundice necessitating immediate transfusion, it is important to determine the hemoglobin content of the blood every six to eight hours the first day and daily for a few days thereafter. Injections of vitamin K and liver extract may be of supportive value. Prophylactic penicillin may be desirable. Theoretical danger of antibody transfer in breast secretions is no longer thought to be a contraindication to breast feeding.

There may be some risk in a small transfusion, beyond that of inadequacy, since adult serum in transfusion may contain sufficient activating substance (conglutinin) to precipitate hemolytic crisis by activating the blocking antibodies coating the red cells of the baby.[10] Exchange transfusion is more efficacious. The dangers must be looked upon as a calculated risk justified by the circumstances.

Exchange transfusion appears to be lowering the incidence of kernicterus and neurological sequelae as much as it is reducing the mortality rate. Intelligence ratings of children who recover from erythroblastosis are only slightly lower than the average.[4] It is so little lower that a physician has warranty for reassuring parents of infants recovering from the disease.

EXCHANGE TRANSFUSION

Factors to be considered in evaluating the status of an erythroblastotic baby are the hemoglobin value in the cord blood, the presence of jaundice, edema, respiratory difficulty, and neurologic abnormalities, the number of nucleated erythrocytes, and the degree of hepatosplenomegaly. There are no infallible rules, but in general exchange transfusion is probably indicated if any two of the following phenomena occur in a baby born to an Rh-negative mother: (1) Positive reaction to the Coombs test; (2) more than five to ten nucleated erythrocytes per 100 leukocytes; (3) hemoglobin content in cord blood less than 16 gm. per 100 cc.; (4) jaundice, or bilirubin content in cord blood over 3.0 mg. per 100 cc.

Infants who have erythroblastosis of the previously mentioned anemic type probably should have small transfusions (10 cc. of whole blood per pound of body weight). However, they should be given an exchange transfusion if respiratory distress develops concomitantly with a rapid decrease in hemoglobin and the number of erythrocytes in the blood.

Routine Rh-typing of obstetrical patients will have accumulated a list of potential Rh-negative donors. There are indications that a female donor is better for exchange purposes.[1] Group O Rh-negative blood which is compatible and shows no sensitization to the Rh antigen is acceptable. It is a probable choice in a rural community. Addition of commercial AB substance may enhance its safety. Fresh blood probably has some advantage over bank blood.

Procedure and Technique

Five hundred cubic centimeters of suitable donor blood is drawn. For exchange transfusion, catheterization of the umbilical vein of the baby is relatively easy during the first 12 to 24 hours. An 18 gauge polyethylene catheter (.067 inch outside diameter) is passed gently through the umbilical vein into the inferior vena cava until a free flow of blood is established. A blunt 18 gauge needle fits snugly in the open end of the catheter and is attached to two three-way stop cocks connected in series. Sterile tubing is connected to each valve, one leading to the transfusion set and the other to a waste receptable. Then 20 to 25 cc. of blood is withdrawn from the baby and discarded. It is replaced with an equal amount of transfusion blood, and withdrawal and replacement then are alternated until 500 cc. has been replaced. This is said to accomplish replacement of 85 per cent of the baby's erythrocytes. To prevent hypocalcemia and tetany due to large amounts of citrate in the transfused blood, 1 cc. of a 10 per

cent solution of calcium gluconate is injected after each 100 cc. of blood is replaced.[9] The apparatus should be flushed with saline solution to prevent clogging. Several syringes should be available. Some physicians advise the use of 0.2 cc. of heparin solution during the first half of the transfusion to prevent clogging.

The umbilical vein may thrombose early. If so, the saphenous vein technique is equally good[2] and is preferred by some investigators. A small incision is made one finger's breadth below the inguinal ligament, midway between the pubic tubercle and the anterior superior iliac spine. After the skin and subcutaneous fat are spread, the saphenous vein may be seen through a superficial layer of fascia. The vein is then isolated and ligated distally and opened gently with a needle or by small incision. The polyethylene catheter is introduced upward for a few inches until there is a free flow of blood. The catheter then is connected with the transfusion apparatus, as previously described, and the exchange is carried out. Replacement transfusion should be done slowly to avoid cardiac embarrassment. The venous pressure can be checked by placing a stainless steel millimeter rule vertically on the baby's xiphoid process and holding the plastic tubing against it. Normal pressures at the xiphoid process are not greater than about 6 cm. of blood. This refinement is not essential if three to four hours is given to doing the transfusion. There should be no hesitancy to discontinue the transfusion if, after infusion of a few hundred cubic centimeters of blood, the baby seems to be in distress.

The feasibility of such a procedure in a small community is illustrated in the following case reports:*

CASE REPORTS

CASE 1. A 34-year-old Rh-negative white pregnant female, married to an Rh-positive husband, had had four previous pregnancies with these results: Miscarriage at three months; term delivery of a stillborn; delivery of a hydropic fetus at eight months; intra-uterine death at six months with maternal blocking antibody titre of more than 1:500.

At eight and one-half months she was delivered of a living female infant with hepatosplenomegaly and, within a few hours, severe jaundice and respiratory distress. In desperation, 450 cc. of Rh-negative, Group O blood was given as a replacement transfusion through the umbilical vein. The baby improved rapidly and at ten months of age was apparently normal.

CASE 2.—A 24-year-old white female, Gravida II, gave a history of 76 hours in labor terminated by high forceps delivery of a living female infant that had severe "birth injuries" and lived a few months in a state of vegetation. The mother, critically ill with bilateral "milk leg," in an emergency transfusion was given a pint of Group O blood not typed for the Rh factor. (The patient had Group B blood.)

Upon the first examination in the second pregnancy (third month of gestation) the Rh-negative status was noted in routine Rh typing. Upon further study the presence of circulating agglutinins was noted. At the seventh month, agglutinating antibody titre was at 1:16 dilution and blocking antibody was up to 1:10. At term, cesarean section was done because the pelvis was relatively small and in light of the previous history. An apparently normal female infant was delivered. Positive reaction to a Coombs test of the cord blood was the only sign of erythroblastosis. However, jaundice began to develop within a few hours, and at ten hours the hemoglobin content of the blood was down to 10 gm. per 100 cc. and the number of erythrocytes had dropped from 4.5 to 3.5 million. An exchange transfusion was carried out. When attempts to get into the umbilical vein were not successful because of thrombosis, the saphenous vein technique was followed. There was progressive improvement after transfusion. Examined at five months of age, the baby seemed to be normal in all respects.

The first of the two case reports illustrates isoimmunization by pregnancy. In the second, sensitization undoubtedly was caused by a blood transfusion. Rh typing should be considered quite as important as blood grouping. No longer can infusions of whole blood without Rh typing be justified. This applies particularly to females before and during the age of childbearing.

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Insulin and Insulin Mixtures—NPH Insulin

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SUMMARY

There are several distinct types of commercial insulins available, and with combinations of these many curves of timing of insulin action may be obtained, but none can parallel the action of a normal pancreas.

NPH insulin, the newest addition, has a wide range of usefulness and may supplant many of the other types and combinations.

SOME diabetic patients may be managed with weight reduction and diet alone; they may need exogenous insulin for short periods of emergency only. Others (approximately 50 per cent of all diabetic persons) need daily injections of insulin. It is the purpose of this discussion to review the types of insulin at hand with special emphasis on the newer NPH insulin.

No matter what theory of the action of insulin is accepted and no matter whether it is believed that diabetes is always caused by a diminished output of insulin from a sick pancreas or by a greatly increased demand for insulin due to overproduction of anterior pituitary and adrenal cortical secretions with final tiring and decompensation of the pancreas, certain facts are axiomatic. The output of insulin from the pancreas of a normal person not only varies from day to day but must vary by several hundred per cent from hour to hour with ingestion of food and physical exercise. This great variation of demand, reaching the pancreas probably both through the blood stream directly with changes in blood sugar levels and through the vagus nerve, is almost unique in the known endocrine system; it is paralleled only by the output of epinephrine (an insulin antagonist) during stress. In light of the sudden outpouring of insulin required after a high carbohydrate meal, the sudden shut-off of insulin as the blood sugar content falls, and the small continued amounts of insulin required to maintain the blood sugar at normal throughout the fasting hours of sleep, is there any wonder that a person with severe diabetes who takes insulin by injection once a day has a tremendous dosage problem?

Best has said, "We hope some day to make the 'ideal' insulin which will be liberated only on response to need so that hyperglycemia and hypoglycemia will be automatically controlled as in the non-diabetic." Today no such insulin is in sight. Furthermore, no matter what theory of the pathologic physiology of diabetes is accepted, it is now axiomatic that the deprivation of insulin, and not excessive carbohydrate intake, brings about glycogen depletion in the liver and causes the development of diabetic ketosis and subsequent acidosis and coma, as was pointed out by Mirsky[5] and others. High blood sugar levels and sugar in the urine are the result of too little insulin activity and are not the primary disease. A realization of these facts must guide physicians in the choice of the type of insulin and the dosage. Moreover, it must temper the desire to keep the patient always sugar-free.

In discussing the choice of the kind of insulin, and even the action of a given type in various patients, another important fact must be recalled. Diabetic persons who need insulin, although all different, fall into two distinct groups. In one group is the patient with diabetes of the mild, stable type usually observed in older persons. His mechanism of response to insulin demand is nearly normal although it cannot take care of the peak demands and eventually insulin debt and pancreatic decompensation will develop. A relatively small dose of any type of insulin will serve his needs. The strain will be off the pancreas and it will have periods of rest when the exogenous insulin carries the load, and will again be able to handle the postprandial peaks. Such a patient will seldom have an abnormal amount of sugar in the blood or have hypoglycemic reactions, and, as long as he keeps his weight down, will do well. In sharp contrast is the severe, brittle, usually young diabetic person whose endogenous insulin response to demand is extremely variable and completely unpredictable and whose exogenous insulin requirements are high. It is in this group that relatively large amounts of sugar are "spilled" even during periods of starvation (overnight); and, as Peck[9] has said, nocturnal hyperglycemia may well signify the existence of a much more serious and hazardous defect than the simple overflow mechanism of postprandial hyperglycemia and glycosuria. In such patients the insulin dosage is tricky, and even multiple injections and insulin mixtures may be ineffective at times.

DEVELOPMENT AND MODIFICATION OF INSULIN

Regular or amorphous insulin developed by Banting and Best[1] in 1922 was life-saving. In action it was potent and dependable. When given subcutaneously, it began lowering blood sugar levels within a period of minutes. The maximal effect was reached in three to four hours and was gone in six to eight hours. One dose a day was sufficient in many of the milder cases but it was soon learned that its action was not prolonged enough in diabetes of the more severe types, in which three to four injections a day

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were necessary. Many attempts were made to slow its action—giving it in an oil suspension was one such attempt—but it was not until 1936 that Hagedorn's modification of adding to insulin a buffered protamine obtained from the sperm of California rainbow trout proved really effective.[3] With that modification, the action lasted well over 24 hours. Later a small amount of zinc was added to protamine insulin by Scott and Fisher[10] to make it more stable and it was found that a single dose would actually carry over a three-day period, approximately 70 per cent being effective the first day, 20 per cent the next, and 10 per cent the third day. This fact is still important in adjusting the dosage of protamine zinc insulin (Chart 1). This new insulin with its slow prolonged action made it possible in many cases to obtain almost complete control of the disease with a single daily injection, and frequently with an actual saving of the number of units needed per day (Chart 2).

In the really brittle cases, however, the action of protamine insulin was too slow, and if enough was given to keep the blood sugar content normal during the day, night reactions were common. Two injections each morning, one of rapid-acting regular and one of protamine insulin, were necessary. Of course the next step was to combine the regular and protamine zinc insulin in one syringe; but at first this met with variable results,[4, 8] until the reason became apparent. Protamine insulin needs approximately 0.65 mg. of protamine per 100 units of insulin to saturate it but it was marketed as a supersaturated solution with 1.25 mg. of protamine per 100 units. So when regular insulin with its acid reaction was combined with neutral protamine in one syringe, even up to unit for unit, the surplus protamine in the solution combined with it to form a more slow-acting (and less dependable) mixture. As the ratio of regular insulin to protamine insulin in the mixture was increased past a 1:1, an insulin that gave rapid but prolonged action was formed.[2, 12] Adding say 40 units of regular to 20 units of protamine insulin produced the effect of 20 units of fast-acting and 40 units of prolonged-acting insulin for night carry-over, although the curve of action of the mixture actually was monophasic. These "tailor-made" mixtures of 2:1 and 3:1 came to be widely used.

Chart 1.—Action of one dose of protamine insulin (50 units) holding the blood sugar content down over 36 hours of fasting.

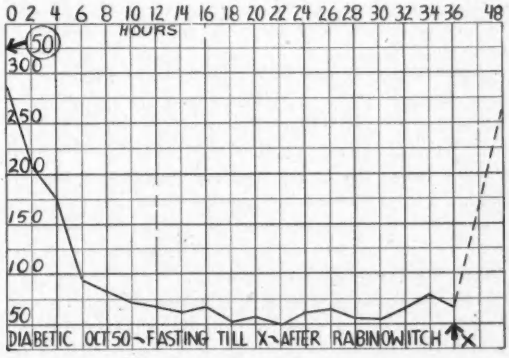


Chart 2.—Action of a single dose of protamine insulin (20 units) on pre-meal blood sugar level as compared with two doses of regular insulin (15 units before breakfast and 10 units before evening meal) with 20 per cent less insulin.

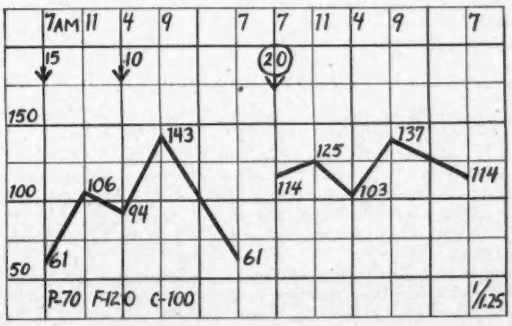


Chart 3.—Action of 40 units of regular insulin and 20 units of protamine insulin in one syringe.

It should be mentioned here that during this transition time crystalline insulin was brought out. Although this is a purer form and therefore causes less allergic reaction, it differs from regular insulin so slightly in action that it may be assumed to be identical in timing.[8] Only economical and technical manufacturing problems keep it from replacing regular insulin on the market. Globin insulin with a maximum action in eight hours and lasting 18 hours[6] controlled some cases of diabetes, but because some patients who used it had afternoon shocks and high blood sugar levels in the morning, it was not universally acceptable and insulin mixtures held the field.

Mixing two insulins in one syringe each morning was a nuisance and for the more ignorant patients and those with poor eyesight was not always accurate. Hence, while the physicians were working out their own particular favorite mixtures, research workers and the manufacturing concerns were working on stable modified insulins, which would give similar results. Many types were tried over a period of years but finally one proved to be the most acceptable. During the period of development it was first called NPC50, then NPH50, and now it has come on the market as NPH insulin. As it is much like protamine zinc insulin in appearance, it is marketed in a square bottle with a distinctive label. This specially modified insulin is a neutral buffered suspension of protamine zinc insulin crystals containing approximately 0.50 mg. of protamine in isophane ratio to 100 units of insulin. It is quite stable. The name comes from: N for neutral, P for protamine, H for Hagedorn and 50 for 0.50 mg. of protamine. In action it is much like the 2:1 mixtures but it is more dependable and more efficient unit for unit. It has a fairly rapid onset of action (two to four hours) and has a good prolonged action of 24 hours or more, insuring an adequate overlap to the next day[7, 8] (Chart 3).

If these points are remembered it is quite easy to change patients to it. If the patient is well controlled on a 2:1 mixture, it is wise to reduce the total units given by 20 per cent the first few days he takes NPH and gradually increase the dosage if he "spills" sugar. As NPH may be a little slower in starting to act, there may be some spillage of sugar after breakfast; but this can usually be controlled by adjusting the diet so that carbohydrate intake at breakfast is reduced and compensated for at other meals. A bedtime feeding is usually wise (Chart 4). Patients with mild cases readily controlled with protamine zinc insulin need not be changed to NPH, but if a switch is desired it may be accomplished without trouble, again cutting the dose 20 per cent at first and watching for insulin shock in the afternoon. In some of the more brittle cases NPH insulin may still be too slow in action. If so, regular insulin may be added to it in one syringe and, as it is not supersaturated with protamine, each unit of regular insulin added will be effective and action such as that of 3:1 or 4:1 mixtures may still be "tailor-made."

Practically all patients taking NPH insulin value its simplicity and state that for some intangible reason they seem to feel better in general. Although there seems to be almost always a saving in the total number of units required daily when switching to NPH, this may be more apparent than real. It must be recognized that in the brittle cases an insulin reaction in the early hours of sleep may not be noted by either the patient or the physician and that such a reaction is frequently reflected in high blood sugar level the following morning. This fasting hyperglycemia then may be erroneously treated by arbitrarily raising the insulin dosage, with the result that the patient is taking far more insulin than is necessary, as was pointed out by Somogyi[11] and others. In such circumstances, if the patient is hospitalized

Chart 3.—Rapid but prolonged action of NPH insulin on the average blood sugar level of six patients (after Peck).

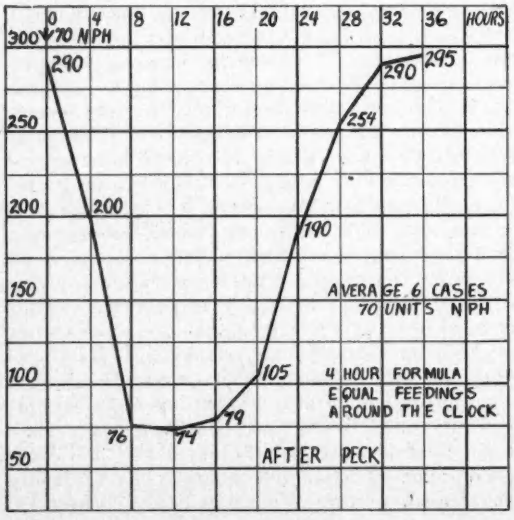
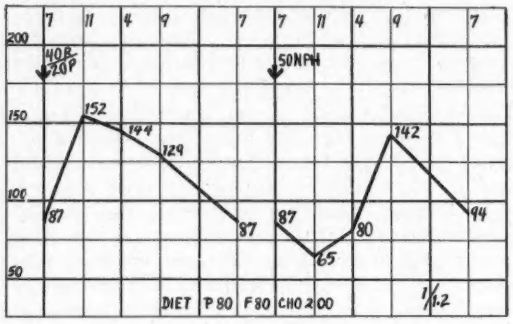


Chart 4.—Action of a single dose of NPH insulin (50 units) on the pre-meal blood sugar level as compared with an insulin mixture in one syringe (40 units regular and 20 units protamine) with 16 2/3 per cent less insulin.



for critical study, it may be noted in switching from one kind of insulin to another that control is obtained with considerably smaller dosage; and from this it may be assumed, falsely, that the kind of insulin to which the patient was switched is more efficient. In any case, NPH insulin is a big step forward and it may be prophesied that it will one day supplant protamine zinc insulin. Regular and/or crystalline insulin will always remain the insulin of choice for use in emergencies.

CONCLUSIONS

The normal pancreas releases variable amounts of insulin from hour to hour to control the ever-changing blood sugar levels. No kind of exogenous insulin in any dosage can possibly parallel this action. Regular or crystalline insulins act rapidly and for short periods. They are the insulins of choice for diabetic emergencies. Protamine zinc insulin bridges over the night but will not prevent postprandial rise in blood sugar levels in severe cases. Daily use of a combination in one syringe of two parts of regular and one of protamine insulin is the most useful insulin mixture.

The newer NPH insulin is a stable, efficient, modified insulin with action like that of the 2:1 mixture. When understood and used with perhaps minor changes in the diet so that carbohydrate intake is properly timed, it will replace all daily mixtures and in time may replace protamine zinc insulin.

Chronic insulin overdosage must be constantly watched for.

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Effectiveness of Smear Technique in Detection of Pulmonary and Gastric Cancer

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SUMMARY

In the initial use of cytologic examination of smears to detect pulmonary and gastric cancer at the Los Angeles County Hospital during the period April 1949 to June 1950, 350 patients with suspicion of pulmonary disease and 128 with gastric problems were studied. In the pulmonary group, 80 per cent of 51 malignant lesions were diagnosed by the smear technique. Sixty per cent of 15 neoplasms in the stomach were diagnosed by the method.

The results are analyzed in terms of sensitivity, accuracy, reliability and "yield" for the method. Cytological criteria of the presence of malignant disease are given and illustrated by photomicrographs.

The method is one of potentially great value as an aid to diagnosis. Use of it in examination of selected categories of patients seems warranted.

SINCE Papanicolaou and Traut[9] in 1943 revived interest in the cytological study of smears of body secretions for detection of exfoliated malignant cells, many investigators have demonstrated the usefulness of this method in the early diagnosis of cancer. The following presentation is a report on the initial routine use of the method at the Los Angeles County Hospital during the period April 1949 through June 1950 with regard to diagnosis of pulmonary and gastric cancer.

MATERIALS AND METHODS

Pulmonary Studies

Smear studies were made in 350 cases. The patients were from various services as follows: Tuberculosis, 56.8 per cent; medical, 26 per cent; surgical, 8 per cent; miscellaneous, 9.2 per cent.

The ideal study was considered to consist of at least two daily sputa following bronchoscopy (or else a series of five daily sputa), but many cases were studied much less thoroughly: Bronchial specimen and sputa, 52.2 per cent; single bronchial specimen only, 23.2 per cent; single sputum specimen only, 14.3 per cent; two or more sputum specimens, 10.3 per cent.

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Presented before the Section on Pathology and Bacteriology at the 80th Annual Session of the California Medical Association, Los Angeles, May 13-16, 1951.

Smears were made directly from aspirated bronchial exudate if there was enough of such material, and if not they were made from material recovered from saline irrigations. Sputa varied in quality but early morning deep cough specimens were requested. During the period of this report, in an effort to build up the cytology service, no specimens were rejected as unsatisfactory. Therefore, many smears which were too thin or which for other reasons would not meet the present standards were included. (At present the general criteria for acceptability outlined by Graham and co-workers[15] are followed. Specimens of sputum that do not contain macrophages are rejected, as are bronchial secretions containing only a few columnar epithelial cells or with only erythrocytes and leukocytes.) In the laboratory, the usual techniques were employed—prompt fixation in alcohol-ether, and staining by the Papanicolaou-Traut method.[9] From three to five smears from each specimen were screened. Abnormal cells were evaluated by the criteria of malignancy as defined by Farber and co-workers.[3]

Gastric Studies

In most of the 128 cases in which smears of gastric material were studied, the patients were subjects for gastroscopy. Thirteen per cent of them were patients in the medical service, 12 per cent in the surgical service, 74 per cent in the gastroenterology clinic, and 1 per cent in other services. Ordinarily the specimen consisted of 20 to 40 ml. of thick mucus aspirated from the fasting stomach via Levine tube for routine gastric analysis preliminary to endoscopy. Smears were made from "fished" particulate matter or, when practicable, from centrifuged sediment. It was not generally necessary to use any adhesive.

As a rule, no pertinent clinical data were available at the time the smears were examined. Liebow and co-workers[6] held, in reference to pulmonary cases, that for a critical analysis of the method, the examiner should know nothing about the patient. Bryant and his co-workers[1] concluded, from a study of gastric aspirates, that this was an added hazard to accurate reporting rather than an aid to scientific honesty. The authors believe that strict adherence to cytological criteria of malignant process, without foreknowledge of clinical data, results in more accurate diagnosis.

REPORTING

If results of examination of smears were positive for cancer, the report given was, "consistent with malignancy." So far as could be determined, there

were no "false positives." Histological evidence of malignant lesion was present in all but two of the 36 proven cases of pulmonary cancer detected by smear (see under *Histology*). If results of smear examination were negative, the report was, "no malignancy." In cases in which "no malignancy" was reported and it was later determined by other means that carcinoma was present, the slides were reviewed. If previously overlooked malignant or suspicious cells then were noted, the original report was considered to have been "false negative." If no such cells were observed in reexamination, the diagnosis was considered "missed." "Inconclusive" was a noncommittal diagnosis; but included among the cases in which the smears were reported as "inconclusive" were some in which there were "suspicious" cells, implying that malignant disease was probable and that examination of additional specimens was important. If malignant disease was found to be present in a case in which the report was only "inconclusive," the result of the smear examination was tabulated as a "miss"; but if the term "suspicious" was used in the report, the presence of the lesion was deemed to have been "detected" by the smear technique. "Misses" in which there were recorded (but unreported) impressions of atypical and metaplastic cells have since been reviewed in terms of Papanicolaou's classification.[7]

The classifications used in the cytologic service of the Los Angeles County Hospital were matched with Papanicolaou's designations as follows:

Los Angeles County Hospital Classification	Equivalent in Papanicolaou Classification
Negative (unequivocally)	I
Negative (with atypical cells)	II
Inconclusive (with atypical cells)	III
Suspicious (probably positive)	IV
Positive (unequivocally)	V

As Papanicolaou's seemed superior to the system in use, it was adopted.

Of the 478 patients studied, 66 had tumors — proven in 49 cases. The 17 cases in which the presence of cancer was still unproven at the time of this report are included for purposes of discussion. Data indicating the sensitivity, reliability and accuracy of the method as it was employed in the period covered by this report are given in Table 1. Table 2 gives data for the separate and combined series (pulmonary and gastric) as to the grouping of the patients examined, sex, and age by decades. The kind of specimens examined is shown in Table 3.

TABLE 1.—*Data on Sensitivity, Reliability and Accuracy of Cytologic Diagnosis of Cancer*

	Total	Pulmonary	Gastric
SENSITIVITY			
Cases studied	478	350	128
Total tumors	66	51	15
"Detected" tumors	50 (75.8%)	41 (80.4%)	9 (60%)
RELIABILITY			
"Missed" tumors	14 (21.2%)	8 (15.6%)	6 (40%)
"False-negative" diagnoses	2 (3%)	2 (3.9%)	0
"False-positive" diagnoses	0	0	0

ACCURACY

Cytologic Report	Papanicolaou Equivalent		Pulmonary	Gastric
"Consistent with malignancy"	V	Detected	38	8
"Inconclusive"	IV	Detected	3	1
"Inconclusive"	III	Missed	1	0
"No malignancy"	II	Missed	3	2
"No malignancy"	I	Missed	4	4

TABLE 3.—*Materials Examined in Attempt to Detect Pulmonary Tumors*

Material	% of patients giving Specimen	% of patients with Tumors	% of Tumors
Bronchial and sputa	52	12	43
One bronchial specimen only	23	21	33
One sputum only	15	12	12
Two or more sputa	10	16	12

TABLE 2.—*Data on Detection of Pulmonary and Gastric Cancer by Examination of Smears*

Service Treating Patient	Total Series			Pulmonary Series			Gastric Series		
	% from Source	% with Tumors	% of Tumors	% from Source	% with Tumors	% of Tumors	% from Source	% with Tumors	% of Tumors
Tuberculosis	43	5.3	15.8	59	5.3	21.5	....	....	....
Gastroenterology	20	3.2	4.5	....	....	....	74	16	100
Medical	23	30	52	27	29	55	13	....	....
Surgical	9	34	23	8	31	17.6	12	....	....
Others	5	4	4.5	6	15	5.9	1	....	....
Sex									
Male	65	17.2	82	70	18.8	90	54	11.6	53
Female	35	7.2	18	30	4.7	10	46	11.8	47
Age by Decades									
0-39	21	1	1.5	21	0	0	20.4	3.8	6.7
40-49	22	10.5	16.7	23	11.2	17.6	19.5	8	13.3
50-59	20.5	17.2	25.7	22	13	27.5	17.2	7.4	20
60-69	22.2	20.7	33.3	21	23	33.3	25	6.4	33.3
70-79	12.2	24.1	21.2	11	26	19.6	15.6	20	26.7
80 and over	2.1	10	1.5	2	2.6	2	2.3	0	0

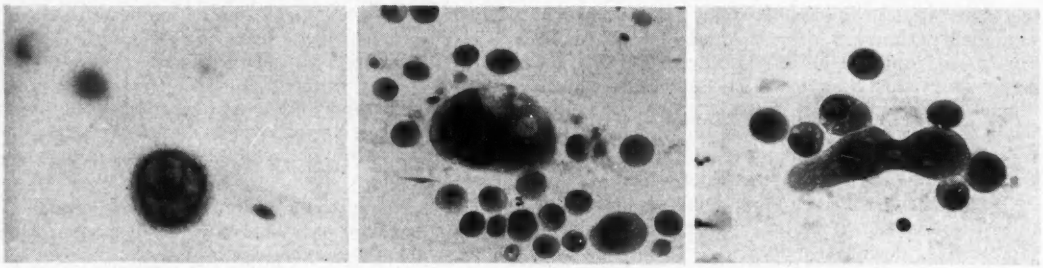

Figure 1. *Left*—A solitary huge malignant cell compared with the normal columnar epithelial cell. Note the nucleus-cell ratio (nuclear predominance), abnormal nuclear clearing ("moth-eaten") and large, abnormally shaped nucleolus. ×1100. *Center*—Multinucleated giant-cell. Note size compared to leukocytes, nucleus-cell ratio, multiple, irregular, crowded nuclei, abnormally large nucleoli, and huge cytoplasmic vacuole. Also note individual malignant cells whose nuclei vary in size, shape and contour with variation of the chromatin granules in size, shape, density and distribution. ×500. *Right*—A cell group. Note crowding, large nuclei varying in size and shape, with increased nucleus-cell ratio, prominent nucleoli, and clumping of chromatin. Also foamy cytoplasm. ×575.

HISTOLOGY

Histologic classification was possible in 46 of the 49 proven cases. The 34 pulmonary lesions are classified below. In one of the two instances in which the type of lesion was completely undetermined, the presence of the growth was proven by pleural metastasis and by x-ray and clinical evidence, and in the other a widespread nonresectable tumor was observed at thoracotomy (the biopsy specimen was lost).

Primary:

Squamous cell carcinoma	25
Adenocarcinoma	2
Unclassified*	5

Secondary:

Adenocarcinoma of pancreatic origin	1
Signet ring carcinoma, source unknown	1

The gastric tumors were adenocarcinoma with the exception of one of the lesions in the "missed" cases, which proved to be a reticulum cell sarcoma. Interpretation of impression smears from the cut surface of the tumor itself was impossible. In one case diagnosis was on the basis of observation, at operation, of a large inoperable posterior gastric tumor with carcinomatosis peritonei, without microscopic biopsy.

CYTOLOGY

Some mention of the most frequently noted features of the tumor cells might be helpful. Single malignant cells rather than groups were commonest among the predominantly squamous, pulmonary cases. However, groups were observed in cases of suspected and proven adenocarcinomata of both pulmonary and gastric origin. Well defined pulmonary types such as Graham's[15] differentiated "fiber" and "tadpole" cells were fairly common, but the most numerous were Graham's so-called "third type." These defy strict definition but they have multiple cytoplasmic and nuclear malignant qualities in varying combinations. Their order of importance among 20 cells photographed as typical examples follows:

1. Increased cell size and irregular shape	14
2. Increased size of nucleus in relation to size of cell (over 1:2 in cells larger than 10 microns)	12
3. Irregular nuclear contour	12
4. Hyperchromatism (especially with abnormally coarse, irregular, unequal chromatin granules, uniformly distributed)	12
5. Abnormally dense cytoplasm	6
6. Abnormal nucleoli	5
7. Vacuolated cytoplasm (not an independent criterion of malignancy, but of corroborative value)	3

The malignant features of exfoliated cell groups are more easily discerned. These were, in decreasing order of frequency, (1) variations in nuclear size, density, shape, and nucleoli; (2) clumping, distinguished by coherence of cells; (3) crowding with mutual deformity of adjacent cells; (4) cannibalism; and (5) malignant pearl formation.

The following examples were chosen for the cytological criteria of the malignant disease illustrated rather than for their clinical or critical value.

CASE REPORTS

CASE 1. A 61-year-old white male with many previous hospital admissions for arteriosclerotic heart disease and pneumonia entered the Los Angeles County Hospital January 4, 1950, with signs of cardiac failure and pneumonia which did not clear. A productive cough was prominent. Body weight declined 20 pounds in the ensuing four weeks. In bronchoscopic examination on February 3, 1950, a thin, sharp, mobile carina was noted. The right main bronchus was normal and there was purulent material in the left. The mucosa was edematous and freely bleeding throughout and the capillary vessels were distended. There was thickening of the spur dividing the left secondary bronchi but report on a biopsy specimen from this area was negative for cancer. A definite pleural exudate was noted on February 7, 1950, and the patient was scheduled for thoracentesis, but died February 14, 1950, before this could be done. Permission for autopsy was given too late. (For cytologic features, see Figure 1.)

CASE 2. A 57-year-old female entered Los Angeles County Hospital June 14, 1950, with complaints of bloating and epigastric fullness with constant pain for four months and ten-pound loss in weight in three months. In x-ray films a prepyloric defect was noted, and in gastroscopic examination a polypoid neoplasm was observed in the antrum on the greater curvature. In smears made at this time malignant

* In two of the five cases the report was "undetermined" from confirmatory biopsy—presumably anaplastic; and in the other three it was "highly anaplastic" at autopsy; "highly anaplastic" in lymph node biopsy, and "probable oat-cell carcinoma" on biopsy.

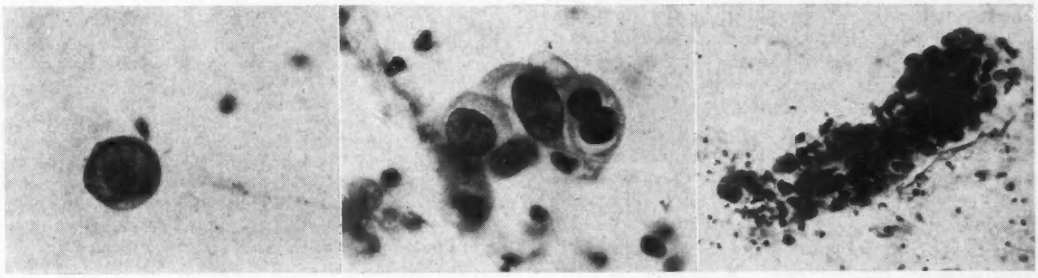

Figure 2. *Left*—A single huge cell compared with the small round cells. Note the nucleus-cell ratio, prominent nuclear membrane, and abnormally cleared areas associated with hyperchromatism, giving a moth-eaten appearance. ×1100. *Center*—Clumped cells. Note coherence, vacuolization, and abnormalities in nuclear size, shape, density, and distribution of chromatin granules. ×1000. *Right*—Large clump with evident coherence, crowding, vacuolization and many aberrations in nuclear details. ×440.

cells and cell-groups were noted (Figure 2). Subtotal gastric resection failed to eradicate a grade IV adenocarcinoma with metastases to regional lymph nodes.

DISCUSSION

Of the many analyses of smear cytology, comparatively few dwell on the clinical usefulness of the method in terms of diagnosis of the presence of pulmonary tumors. Watson and co-workers[16] studied 1,200 cases, in 236 of which there was bronchogenic carcinoma. Of the total 141 were detected by the smear technique, a "yield" of 8.5 per cent for the series. Farber and co-workers[2] reported positive diagnosis by examination of smears in 9.8 per cent of cases in a series of 2,066.

Liebow,[6] in a review of pulmonary cases, considered the omission of the large proportion of cases in which there was no cancer improper for a truly critical analysis. Not to enter this controversy, the present report is presented to show that worthwhile "yields" may be anticipated by this method applied to selected groups of patients. Its obvious limitations as a mass screening test, in comparison to chest x-ray, for example, have led many physicians to reject it as altogether valueless.

The demonstrable increase in pulmonary carcinoma,[12] 0 to 2.3 per cent from 1918 to 1946, and the virtually assured 2 per cent incidence of gastric cancer in patients examined postmortem in the Los Angeles County Hospital, emphasize the value of a test which, even when incidentally employed, detects cancer of the lung in 80 per cent of cases in which such lesions are present, and gastric cancer in 60 per cent. The results reported herein, admittedly fortuitous, and also those of more experienced workers,[13] indicate that with practice and conservatism, the one great hazard of false positive diagnoses may be practically eliminated.

Ferguson[4] expressed the opinion that false-positives should be expressed as a percentage of the total positive reports, rather than of the total series. Thus, three false-positive and seven true diagnoses out of 100 cases would be 30 per cent instead of the customary 3 per cent. This would appear to be simply a matter of definition of terms in a survey of essentially normal individuals, but in a practice in which many of the patients have non-cancerous disease characterized by atypical and metaplastic cells, such a classification seems unfair. The pathologist who must distinguish between the abnormal cells of bronchiectasis and those of malignant tumors is not faced with the simple dichotomy, is it cancer or is it normal? Rather, the problem is, is the abnormality malignant or is it benign? Lesions which may be biopsied only by expert endoscopists, if at all, may often be detected by examination of specimens which can be obtained without special equipment or skill and with a minimum of patient cooperation.

Graham and co-workers[15] expressed belief that sputum has distinct advantages over bronchial secretion: "The laboratory can exercise more rigid control over the preparation of the smear. Repeated specimens of sputum can be obtained with greater ease. Finally, patients presenting definite enough symptoms to justify bronchoscopy have, too often, far advanced disease."

Watson and co-workers[16] compared the 60 per cent accuracy of smears (112 sputum and 29 bronchial secretions "positive," out of 236) in bronchogenic carcinoma with 36 per cent "positive" biopsies on bronchoscopy (63 out of 176), and 86 per cent "positive" aspiration biopsies (85 out of 98). In 18 cases, seven of which proved operable, the preoperative "histological" proof depended upon cytology alone. In the series here reported upon, two cases were diagnosed by smear in the presence of "negative" biopsies, and the presence of malignant lesions was later proven by operation and autopsy. Herbut[5] reported a series of 118 cases of pulmonary carcinoma in which 32 (27 per cent) were detected by smear but missed on bronchoscopy. In the present series the results with sputum alone (14 per cent yield) appear poorer than with a single bronchial specimen alone (21 per cent yield). However, the disproportionately great number of patients with tuberculosis in the series (59 per cent) distorts the relationship. Later experience has led to the conviction that a series of at least five specimens of sputum is superior to bronchial secretions. The 80 per cent over-all smear sensitivity which the authors claim for a series including some histologically unproven cases is less than the 89 per cent of Herbut,[5]

about equal to the 80 per cent of Farber[2] and somewhat higher than the 60 per cent of Watson and co-workers.[16] Therefore, if 14.6 per cent of a selected group of patients harbor pulmonary tumors, of which 80 per cent are detectable by smears, prepared only incidentally in connection with another procedure and collected in part in an indifferent fashion, how much more valuable might this service become with increased ability on the part of the laboratory and increasing interest on the part of the clinician?

The difficulties in the cytological diagnosis of gastric cancer are suggested by Richardson's[11] observation that by using a cyto-histological preparation of gastric washings, he can distinguish acute, chronic and atrophic gastritis, ulceration and carcinoma. He reported an accuracy for carcinoma of 48.1 per cent with 3.9 per cent "false positive." Ulfelder and co-workers[14] successfully diagnosed, by smear, 12 out of 14 cases of gastric cancer proven at operation. Pollard and co-workers[10] reported that in a series of 278 cases in which there were 41 histologically proven neoplasms, they successfully diagnosed 35 per cent by smear, with 12 per cent indefinite. Bryant, Craig and Pollard[1] reported positive diagnosis in 41 per cent of 61 cases in which there was histological proof of cancer. In the present series the diagnosis of 60 per cent of the 11.7 per cent of malignant tumors in a selected group of patients is conditioned by the facts that in two cases anatomical proof was lacking, and one of the "missed" lesions was an undiagnosable reticulum cell sarcoma. It is apparent that much less accuracy and reliability is possible with gastric smears than with pulmonary. However, considering the simplicity of the test in comparison with gastroscopy and x-ray study, and the admitted unreliability of all three methods in establishing the malignant nature of a lesion, it seems reasonable to employ smear examination equally, as a source of corroborative information at least.

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Enuresis

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SUMMARY

Enuresis is a symptom rather than a disease. It may occasionally be the result of an organic condition but most cases are functional in origin. The organic cases are rather simply classified, the diagnosis should not be difficult, and the treatment is fairly well standardized. The functional cases, on the other hand, are of a variety of types which tax the physician and the family in understanding and treating the problem.

The author presents some of the known facts about enuresis and discusses the accepted forms of therapy. An important requirement is a better understanding and study of the child from the medical, psychological and environmental viewpoint. In this way a more rational therapy may be advised.

ENURESIS occurs relatively frequently in children and occasionally in adults. By strict definition, enuresis is an involuntary discharge of urine. That this broad interpretation is followed by many authors and investigators is apparent from a survey of the literature. Without engaging in a discussion of semantics, it is obvious that some orientation must be undertaken before the subject can be profitably discussed.

The first step in an understanding of this problem is to review briefly the generally accepted physiology of urination. Nervous control of the bladder consists of a spinal reflex and a suprasegmental conditioning reflex. The normal stimulus for the reflex is the filling of the bladder until proprioceptive impulses have reached a sufficient threshold to produce discharges of the motor neurones, which results in voiding contractions of the bladder. The infant bladder is controlled by a simple spinal reflex arc synapsing in the sacral cord. As the infant develops into childhood, this purely uninhibited behavior of the bladder gradually comes under control of the suprasegmental mechanism and thus under direction of the higher centers. This integration should take place by the third year and it is at this point that the child should acquire control of the urine (Nesbit[12]).

If the broad definition of enuresis as an involuntary discharge of urine be accepted, then it is correct to postulate that anything which interferes with normal inhibitory control of the bladder should be classed as enuresis. Obviously this covers a large territory of conditions and some systematic classification is necessary to proper understanding of the problem.

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CLASSIFICATION OF DISORDERS

In the first general division, it is necessary to differentiate between organic and functional enuresis. Many investigators would exclude from consideration as a part of the enuresis problem those cases in which there is organic cause of incontinence. It would be much simpler to agree with this premise. On the other hand, the finding of organic disease processes within the enuretic group may well explain the additional amplitude given to the stimuli which results in the suppression of the inhibitory mechanism, thus permitting the bladder to empty involuntarily by means of the spinal reflex.

At the same time it should be agreed that incontinence and enuresis are not equivalent terms. Incontinence is present in many disorders but is not a constant finding in all cases in which the disorders exist. Incontinence is usually considered as the overflow dribbling of a decompensated bladder which has lost the ability to function normally due to a breakdown of its neuromuscular mechanism.

If the organically caused cases be accepted as within the range of enuresis—and the author believes this is necessary in order to fully appreciate the problem—it is consistent to classify these cases as, urological, neurological, and general.

Urological disorders account for the bulk of the cases within the organic group. These have been studied and enumerated by many investigators. The excellent review by Campbell[3] presented the wide variety of lesions which extend from the external urinary meatus to the kidney. (The author's experience, in a more limited series, parallels the findings of Campbell.)

Neurological disorders may be any of a variety of conditions in which urination is not under voluntary control. Many of these conditions are true incontinence and should be excluded. Some may be classed as enuretic conditions.

General physical disorders are found in cases of enuresis. These may be gastrointestinal disease, nutritional disorders, acute infectious processes, and endocrine disturbances, to mention only a few. As Townsend[17] pointed out, "We must be on the alert lest some incidental abnormality be given etiological significance." It must be remembered that the enuretic child who has achieved control may undergo relapse during any illness.

FUNCTIONAL DISORDERS

By far the preponderance of enuresis falls within the functional or psychogenic group. The variety of etiological factors and the wide range of classifications which fill the literature depends largely upon which psychiatric school of thought gives rise to them. Certainly all functional cases are not of the same degree of severity. Some attempt at clarification must be made.

A simple classification is that advanced by Townsend,[17] who divided this group into: (1) *Habit disorders*, (2) *conduct disorders*, and (3) those in which there are *psychoneurotic symptoms*.

The *habit disorder* is illustrated by the child who, through neglect and lack of training, does not mature at the average rate and clings to infancy instead of growing up.

The *conduct disorders* are those which, for example, exist in children who adapt enuresis as a means of defiance, hostility, and retaliation toward parents or siblings.

In the group with *psychoneurotic symptoms* are children who progress from the symptoms found in the habit disorders to obsessional and compulsive defenses. Such children often have changes in personality structure. Enuresis on this basis is by far the most serious and refractory. Boys in this classification often are weak, passive, infantile persons who usually remain effeminate and do not mix with other boys of their own age. Girls, on the other hand, are frequently active and aggressive, and in them enuresis represents a revolt against the passive feminine role. This probably accounts for the greater incidence of cure seen in girls with the approach of adolescence.

Enuresis is now considered by most investigators to be a symptom rather than a distinct disease entity. Thus, it takes its place as an important complaint in the review of a patient who has a complexity of conditions, be they organic or functional. For this reason, the history in such cases is of primary importance. How long has the child been affected? Has he ever established normal voiding habits? Is he enuretic during the day? Does he experience discomfort, or have difficulty, in voiding? Does the child react normally for his age to his surroundings, or is he emotionally retarded or abnormal? What is the emotional environment of the child, both with regard to parents and siblings? And, above all, what is the reaction of the parents to this problem? Are they interested, annoyed, overanxious, or just plain bored? All of these factors should be worked out in meticulous detail. In many cases, the history itself will give the lead which will make it possible to classify the child and open up the proper avenues of treatment. The importance of the history will be recognized when a few of the known facts about enuretic persons are considered.

Enuresis is of higher incidence in boys than in girls. It often disappears with adolescence. It is rare in adult women, but experiences in both of the world wars emphasize that the condition is present in adult males in greater proportion than might be suspected in usual practice (Shlionsky,[14] Levine,[10] Higgins,[9] and Cohen[5]). This is due, no doubt, to reticence in seeking medical advice for what is usually considered to be a childhood disorder.

Race and color have no significance. Enuresis has been observed in persons on all economic levels of society. In children, there seems to be no correlation with intelligence, although in the armed services enuretic adults seemed to be below average in educational and occupational background (Anderson,[2] Stockwell,[16] Campbell[3]).

There seems to be a familial tendency to enuresis, and siblings are often affected (Frary[7]).

Parental maladjustments as well as the parental attitudes toward the problem have a definite effect upon both the cause and the control of enuresis.

Depth of sleep has long been considered a factor. It is very difficult to evaluate. Most of the recent investigators discount the importance of variations in sleeping habits (Courtin[6]).

From the psychological viewpoint, it is well to remember that enuresis is a symptom which centers attention upon the child. The response by the child to the attitude of the parents is usually in direct proportion to their reaction.

As has been pointed out by Smith:[15] "More fears, jealousies, and worries are found among enuretic children than among others. On the whole, they get into more behavior difficulties and have more nervous habits than do dry children. We have no positive proof that the parents of bedwetters, as a group, are more lacking than other parents in those traits which endear them to their children, but clinical studies lead us to believe that this is true. It is the spirit that exists in the household that has most to do with producing dry or wet beds. Until a child feels inner security he is hard to cure and always ready to relapse."

EXAMINING THE PATIENT

Examination of enuretic children should be thorough. If an organic background is suspected, this avenue of approach must be carefully explored. In cases indicating urologic disease all portions of the urogenital tract should be scrutinized. This must include cystoscopy and regional x-ray studies (Campbell[4]). As greater proficiency in cystometry is developed, this may prove of value in cases involving bladder dysfunction. In cases falling within the neurological group, evaluation of these disorders may usually be accomplished by careful examination. In general disorders it is necessary to determine what part the illness plays in enuresis.

If the enuresis proves to be functional, then careful evaluation of the child must be undertaken. This must include a study of his environment, habits, personality, and his reactions and relationship to parents, attendants and siblings. A careful consideration of the parents with an insight into their background and psychological makeup is often necessary to fully evaluate the reactions of the child.

After the child has been surveyed from physical, emotional, and environmental viewpoints, it is possible to offer some advice which will help him to gain and maintain vesical control.

In cases in which organic processes have been found, these conditions must be treated and, if possible, cured. If the child has developed a habit pattern of enuresis during physical illness, this of itself may have to be treated once the organic lesion has been eliminated.

The simple routine of being "taken up" at night has "house broken" most children. How well and how intelligently this is done will be the index of success. This develops a conditioned reflex which, when integrated with the inhibitive suprasegmental mechanism, will usually result in normal toilet habits. Great care must be exercised in the early "breaking" period. All too often the seemingly frenzied desire on the part of the mother to get her youngster housebroken will result in psychological damage to the small child.

Investigators who have studied the enuresis problem have, from long experience, arrived at certain conclusions regarding the methods which have proved useful in establishing good toilet habits. First, the child must fully understand the problem and what is to be done about it. Second, he should take the initiative in planning the routine and carrying out the procedures. Third, he must have willingness to do it.

In the earlier years, the periodic awakening will need to be done by the parents. It is often helpful for the father to assume this responsibility. As soon as the child can get up by himself, arrangements should be made for him to do so. This may be accomplished by the use of an alarm clock, which the child should wind and set himself. The use of the Mower[11] apparatus, which causes a bell to ring as soon as a pad within the child's bed becomes wet with urine, may be helpful.

The child must be fully awakened before he goes to the toilet. Oftentimes this requires various stimuli such as a period of play, brushing of the teeth, or even a bath. Sometimes rewards are useful. As the child becomes interested in the game of getting up and going to the toilet, his response will increase.

The child should make the trip to the bathroom by himself. This will increase his own response to the training and make him feel that he, himself, is playing the major role in this new game of staying dry.

All of these aids and routines depend largely upon the child's own desire to stay dry and the feeling that this is being carried out through his own initiative and effort. The more this training period becomes a game, the quicker will it produce results. The attitude of the parents should be that of interested spectators, ready to praise when there is success and never condemning when there is failure. The use of a calendar with gold stars for dry nights is in keeping with the game-reward idea, which is infinitely more successful than punishment or harsh words.

Drugs have been used for centuries to induce children to remain dry. At about the time Columbus discovered America, bed wetting was being treated by "the scattering of dried and tricturated cock's comb on the bed of the bed wetter without his knowledge" (Seelye[13]). A multitude of remedies has been used. The success of these is in direct proportion to the degree of confidence the child develops in himself and in his counselor or physician and in the massive doses of suggestion that accompany the drugs (Campbell[3]).

Atropine is the most widely used drug and is usually given for its antispasmodic effect. Pharmacologically it is indicated only in cases of parasympathetic imbalance, where the emptying mechanism of the bladder is in control. Amberg[1] has shown that atropine may reduced the height and rate of vesical contractions, thus allowing the bladder to retain more urine. It is conveniently administered as tincture of belladonna and should be used until the physiological effects of atropine, flushing of the face, acceleration of the pulse or dryness of the throat occur. Atropine is contraindicated in cases of sympathetic imbalance in which the bladder is atonic and the sphincter is not relaxed.

With the thought that depth of sleep was an important factor, some investigators have used stimulating drugs such as caffeine and, more lately, Dexedrine.® These should be employed with caution.

The use of sodium chloride before bedtime is based on the theory that concentration of the urine will make bedwetting less likely. Its irritating effects upon the stomach and the increase in thirst following its use should be sufficient cause for its abandonment. It is still being widely used with little results.

Limitation of fluids during the evening seems quite logical. A relatively dry, easily digested supper, with avoidance of such fluids as tea, coffee, and even chocolate, has been prescribed for generations. This is an empirical prescription; there is little scientific basis for it.

As enuretic children often void more frequently during the day than other children, it is well to encourage them to hold the urine as long as possible during the daytime. There is some evidence, not very scientifically established, that enuretic children have a smaller bladder capacity than normal children (Hallman[8]).

For cases of enuresis which persist into adult life, more exacting treatment is required. In many instances an organic basis will be noted, and treatment by a urologist or neurologist may be indicated. If there is no organic cause for the enuresis, careful psychiatric treatment is usually necessary.

Scientific medicine is not growing simpler. As each new problem arises, physicians must expand the horizon of knowledge to meet the changing order. The enuretic child has received all too scant attention. Physicians have been content to rely mainly upon the approach of adolescence for the cure of this distressing symptom.

To the author it seems that no one is in a better

position to help enuretic children than the family physician. He knows their background, the family problems, the history of the child, often from its birth. No one may so easily gain the confidence of the child and of the parents. At times he will need the aid of ancillary services. Often by his own wisdom, tact and patience, he can help these unhappy children to resolve their problems and to guide them from the wet nights of babyhood into the exciting days of adolescence.

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Primary Postpartum Hemorrhage

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SUMMARY

Postpartum hemorrhage is the outstanding cause of maternal mortality, and a redoubtable contributor to puerperal death from other causes, notably infection and renal failure. The clinical situations in which hemorrhage is liable to occur must be better known, so that anticipatory and preventive measures can be taken. Recent knowledge about defibrinated blood in women with degenerative changes at the placental site must be incorporated in the thinking and practice of physicians dealing with obstetrical cases. The indications, limitations, and hazards of the various anesthetic methods available for parturient women should be carefully considered in the circumstances of each case.

PRIMARY postpartum hemorrhage is excessive bleeding from the genital tract during the first 24 hours after birth. A blood loss in excess of 600 cc. is usually regarded as hemorrhage. The bleeding may occur before or after the third stage of labor is completed. Although the blood loss is usually external, in certain instances it may be more or less concealed. The bleeding may be sudden and furious, erratically repeated, or a slowly exsanguinating trickle. It may follow spontaneous or operative vaginal delivery, cesarean section, or cesarean-hysterectomy. Postpartum hemorrhage occurs in approximately 5 per cent of all deliveries. Puerperal hemorrhage after the first 24 hours is known as *late postpartum hemorrhage* and has been considered elsewhere.[6]

There are both immediate and delayed hazards in postpartum hemorrhage. The immediate threat is death from loss of blood and irreversible shock. Delayed complications are puerperal infection, transfusion reactions, renal failure from lower nephron nephrosis or cortical necrosis, thromboembolic disease, and finally, Simmonds' disease, or pituitary cachexia.

Most cases of postpartum hemorrhage can be anticipated, more can be prevented, and all can be treated. No woman should die of hemorrhage, the number one cause of maternal mortality, and a formidable contributor to puerperal death from other causes. The best treatment for postpartum hemorrhage is its anticipation and prevention. The several major causes of postpartum hemorrhage, although generally known, are here considered in the light of present knowledge:

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Uterine Atony

Myometrial exhaustion, or what is more commonly called uterine atony, is undoubtedly the most frequent cause of postpartum hemorrhage. The usual predisposing factors are prolonged or precipitate labor, overdistention of the uterus, antepartum hemorrhage, deep anesthesia, and mismanagement of the third stage. Prolonged labor is usually owing to cephalopelvic disproportion, to uterine inertia, or to the premature and injudicious use of analgesics or conduction anesthesia. Cephalopelvic disproportion should be recognized in good time, and never permitted to eventuate in desultory labor. Primary inertia should be treated by support and stimulation, in contrast to secondary inertia which should be managed by rest and sedation. Labor can be prolonged many hours by starting continuous caudal analgesia prematurely; labor can be brought to a complete standstill for hours by the untimely administration of "terminal" spinal anesthesia. Postpartum bleeding is almost inevitable after the relaxation induced by deep anesthesia, particularly ether. Uterine atony follows precipitate labor just about as often as prolonged labor; and one should be cautious about the induction of labor, as induced labor is often prolonged or precipitate.

Overdistention of the uterus from multiple pregnancy, hydramnion, or excessively large fetus, is notoriously liable to be followed by postpartum hemorrhage. In such circumstances, the uterus should be decompressed slowly and general anesthesia used cautiously. Cross-matched blood should be in readiness.

Trauma of Delivery

Injury to the uterovaginal tract continues to be a major cause of postpartum hemorrhage. The anatomical lesions are cervical and vaginal lacerations, including rupture of the vagina, paravaginal hematomas, and rupture of the uterus. With most of these accidents the bleeding is external, in contrast to the more or less concealed hemorrhage which occurs with ruptured uterus and paravaginal hematomas. The external bleeding is typically a slow, steady trickle of bright (arterial) blood, in distinction to the darker blood which escapes from the placental site. The possibility of these complications should be thought of after precipitate delivery, after difficult obstetrical maneuvers, and with the parturition of elderly primiparae.

Laceration of the cervix is inevitable if delivery is attempted through an incompletely dilated os. Manual or digital completion of dilatation has no place in modern obstetrics; if conditions are propitious for vaginal delivery except for a persistent

remaining ring of cervix, Dührssen's incision should be made. The first clue to a contracted midpelvis may be brisk bleeding from puncture wounds over prominent ischial spines. Lacerations of the vaginal vault are not uncommon after breech extraction, forceps rotations, and the inept use of Kielland forceps. A rotary or torsion force may actually rupture the vagina (colporrhexis) by creating a circular tear around the cervix, usually in the posterior fornix, which communicates with the peritoneal cavity. The bleeding with colporrhexis is usually furious because of laceration of the internal pudendal, middle hemorrhoidal, or vaginal artery. No woman should be returned to bed if there is a steady trickle of blood. The cervix and entire vaginal vault should be inspected if there is suspicion of trauma. Sometimes a physician has to rely on tactile sense to locate a laceration which is hidden by the invagination of its edges. Lacerations should be visualized (or palpated) and promptly repaired. A gently placed vaginal pack is often adequate for superficial abrasions, but if the vagina is packed too tightly bleeding may be aggravated by forcing the ends of the severed vessel apart; moreover, overpacking the vagina may cause neurogenic shock. In rupture of the vagina, if hemostasis cannot be obtained per vaginam, ligation of the hypogastric artery may be necessary.

Vulvovaginal and paravaginal hematomas are not uncommon and are usually not preventable. Backbleeding from a retracted submucosal vessel in the episiotomy or a laceration is the usual mechanism. By starting the repair two centimeters above the apex of the episiotomy or laceration, the likelihood of "missing" a submucosal vessel is lessened. Hematomas should be recognized early, evacuated, and bleeding points secured. If the process is left to nature, the extravasation of blood may extend past the broad ligament to the lumbar plate.

Traumatic rupture of the uterus occurs much more often than vital statistics would indicate. Deaths attributed to "obstetrical shock" are often due to unrecognized or disavowed rupture. Rupture should be thought of after every difficult forceps delivery, version and extraction, and breech extraction.[2] If there is any doubt about the integrity of the uterus, manual exploration should be done. If rupture is noted, the uterus should be packed, and a continuous transfusion given until arrangements are completed for laparotomy. Hysterectomy is necessary in about half of such cases, although in many instances the uterus can be saved by repairing the rent.

Errors of the Third Stage

More women die during the third stage of labor than during the first two stages combined. Proper management of the third stage is perhaps the obstetrician's greatest responsibility. The third stage is all too often the fatal climax of a neglected first stage and a traumatic second stage worsened by the effects of injudicious anesthesia. Full description of the proper management of the third stage cannot be undertaken here, but this much should be said: The conduct of the third stage should begin during the second stage by the deliberately slow delivery of the fetus to allow time for the uterus to accommodate itself to its diminished volume and thus peel off the placenta in a physiological manner. The Credé maneuver is dangerous and obsolete. No attempts to deliver the placenta should be made until it has separated, and the fundus is firmly retracted. Squeezing or kneading the uterus traumatizes the myometrium, dislodges thrombi from the placental site, and invites inversion. If and when deep anesthesia is used, it should be stopped the moment the fetus is delivered. Mismanagement of the third stage of labor was responsible for four out of seven cases of acute or subacute inversion recently reported from the Sloane Hospital for Women.[4] Vigorous bleeding at any time calls for immediate extraction of the placenta. In addition to massage, bimanual compression, and use of oxytocics, manual exploration should always be done if bleeding persists after the placenta is out, and it should be done before a tampon is placed. Retained placental tissue, a submucous myoma, rupture or inversion may be noted.

An emergency unit of type IV(0), Rh-negative blood should be kept refrigerated on every lying-in suite. The equipment necessary for laparotomy should be immediately available in or adjacent to the delivery pavilion. It is well to transfer postpartum women to a recovery room for the first 24 hours, so that they may be observed constantly by competent personnel. This would do much to prevent serious secondary relaxations, and the "floodings of the newly laid women."

Defibrinated Blood

Thanks mainly to the Boston group of obstetricians, more and more is being learned about the development during pregnancy of conditions making the blood incoagulable. Many physicians have observed cases in which the patient bled to death because the blood had lost the ability to clot. Hemorrhage not only from the placental site, but from surgical incisions, venipunctures, and even from the nasopharynx has been observed; and in such instances death may have occurred despite heroic measures, including ample blood replacement and hysterectomy. Since the report of Maloney and his associates[5] in 1949 a significant literature has accumulated on the subject of acquired afibrinogenemia of pregnancy. It is now known that whenever there is necrosis or degeneration at the placental site, there is a chance that particulate matter, thromboplastin, toxins, and anticoagulants can be absorbed into the maternal circulation. In extreme cases the woman's blood may become totally defibrinated and quite incoagulable. The hematologic findings include critically low values for fibrinogen and prothrombin, and often a circulating fibrinolysin is present. A sample of such venous blood when incubated will either not clot at all, or else the clot will be so fragile that the slightest vibration will cause it to disintegrate. When the plasma fibrinogen level is reduced from

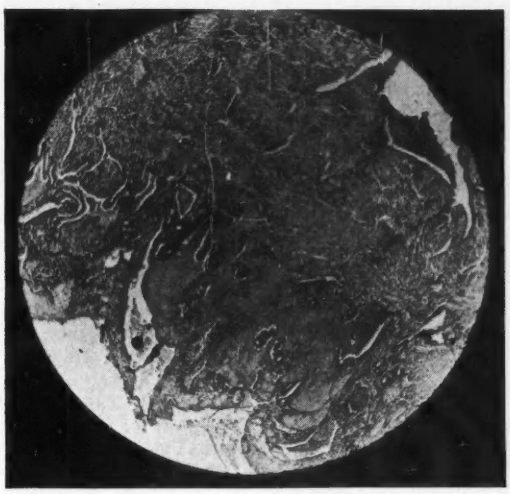

Figure 1.—Placental site six hours postpartum. Hysterectomy done for intractable hemorrhage due to afibrinogenemia. Note sinuses filled with liquid blood. × 17.

the normal concentration of 0.5 gm. per 100 ml. to 0.2 gm. per 100 ml. the circulating blood is incoagulable.

It is now known that abruptio placentae, fetal death in utero, toxemia of pregnancy, and sometimes placenta praevia may be associated with defibrination of the maternal blood, depending upon the absorption of anticoagulants into the circulation. Women with these complications should be studied hematologically as well as obstetrically. In addition to replacement of whole blood, specific deficiencies of fibrinogen and prothrombin must be eliminated if uncontrollable postpartum hemorrhage is to be averted. Fibrinogen in the form of Fraction I, from which the virus of homologous serum jaundice has been removed by nitrogen mustard, is packaged in flasks of 2 gm. (2,000 mg.), and may be dissolved in 300 to 500 cc. of 5 per cent glucose or normal saline solution for intravenous administration.[3]

It is important that a uterine bag, or metreurynter, not be used in such cases. A uterine bag makes a closed system, so that when contractions begin, particulate matter, break-down products and anticoagulants are swept into the maternal sinuses, thence into the circulation, with risk of sudden death from amniotic fluid embolism, or aggravation of the incoagulable blood status. Simple rupture of the membranes, and the draining off of amniotic fluid with its noxious compounds, is a rational precautionary measure, and should be done when feasible.

In a recent case in which antepartum fetal death occurred at six months due to the Rh-factor, afibrinogenemia developed in the patient during the four weeks that the dead fetus was carried in utero. In examination of the specimen obtained at hysterectomy, which was six hours postpartum for intractable hemorrhage, unclotted blood in the placental sinuses was observed (Figure 1), and there were extensive degenerative changes in the trophoblastic-

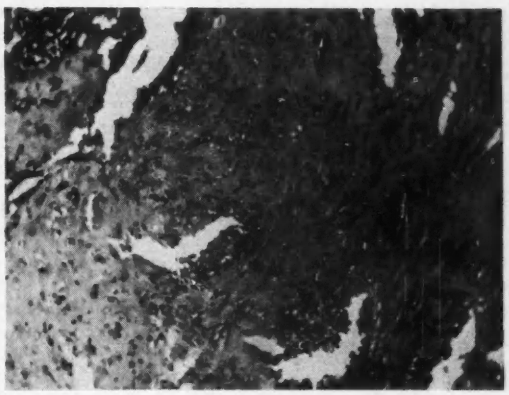

Figure 2.—Decidua basalis of same specimen as Figure 1. Note extensive necrosis of the decidual cells and round cell infiltration. The dead fetus had been carried in utero for four weeks prior to delivery. × 43.

decidual junction (Figure 2), the source of the anticoagulants. Even though the placenta had been implanted high in the corpus the patient was admitted in early labor with prolapse of the placenta, no doubt due to the combined effects of necrosis of the placental site plus Braxton-Hicks contractions. In microscopic examination of the placenta (Figure 3) endarteritic obliteration of the villous vessels and atrophy of the chorionic epithelium were noted. Venous blood drawn at the time the patient was admitted to hospital did not clot even after five days.

Antepartum Hemorrhage

Antepartum bleeding predisposes to postpartum hemorrhage. The value of prophylactic blood transfusions in cases of placenta praevia and abruptio placentae was emphasized as long ago as 1919 by Bill[2] of Cleveland. The vicious circle of bleeding followed by uterine relaxation, followed by more

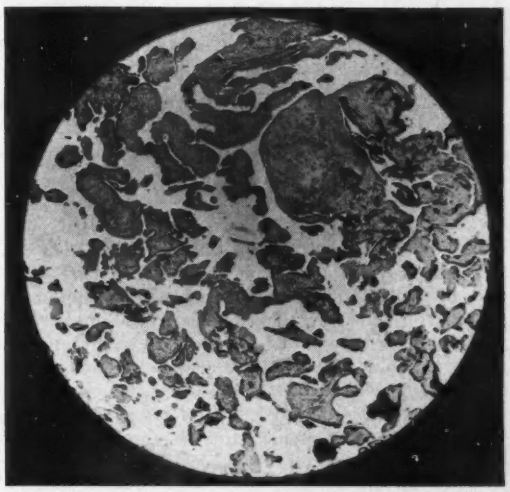

Figure 3.—Chorionic villi from same case as Figures 1 and 2. Placenta gradually became detached and eventually prolapsed. Note disappearance of chorionic vessels and epithelium. × 100.

bleeding until irreversible shock sets in, should be anticipated, and never permitted to occur. Blood lost antepartum should be replaced antepartum or intrapartum to prevent postpartum hemorrhage.

The interests of mother and fetus will best be served in cases of placenta praevia and abruptio by ample blood replacement, and simple rupture of the membranes, or cesarean section, depending upon the particular case. The author regards the use of dilating uterine bags as dangerous in either complication. In both conditions there is the risk of amniotic fluid embolism and of provoking the defibrinated blood syndrome. In placenta praevia there is the added hazard of furious postpartum hemorrhage from a laceration of the friable cervix or bleeding from a sinus in the placental site due to the trauma of a dilating bag. A bleeding sinus in the lower segment encountered at cesarean section can be visualized and transfixed. In both placenta praevia and abruptio placentae, hysterectomy is occasionally necessary as a life-saving measure.

Toxemias of Pregnancy

Postpartum hemorrhage should be anticipated in all cases of "toxic" pregnancy, for the following reasons: (1) Vasomotor collapse with consequent uterine atony and hemorrhage frequently follows delivery in such cases, for the vasomotor response to emptying the uterus is unpredictable. Therefore, spinal and general anesthesia should be avoided; local infiltration is preferable. (2) Often in "toxic" pregnancy there are degenerative changes at the trophoblastic-decidual junction, and the risk of defibrinated blood is considerable. (3) As was first pointed out by Slemons[8] in 1933, in toxemia of pregnancy the myometrium may be diffusely infiltrated with intermuscular hemorrhages identical with those observed in cases of abruptio placentae. A uterus thus affected may not retract postpartum, and hysterectomy may have to be done. In the case reported by Slemons, hysterectomy was necessary nine hours after cesarean section, because of repeated severe hemorrhages due to a blood-infiltrated myometrium.

Uterine Tumors

Uterine neoplasms are only rarely a cause of postpartum hemorrhage. Multiple intramural myomas or extensive adenomyosis[9] may interfere with proper retraction. More important, however, is a submucous myoma which has undergone red degeneration. Such a myoma can become agglutinated to the placenta, and prevent its complete separation in the third stage. If, upon inspection of the delivered placenta, a clean, punched-out defect is noted, a submucous myoma should be suspected and manual exploration carried out. Exceedingly rare causes of postpartum bleeding are cervical carcinoma, cervical polyps, ectopic decidua[7] which may involve the cervix, and hemangioma of the uterine wall.

Cesarean Section and Cesarean-Hysterectomy

Postpartum hemorrhage is a major cause of death following cesarean section. It is probable that the blood loss frequently amounts to between 500 and 1,000 cc. The sources of bleeding are the uterine incision, including transection of the uterine vessels on one side, unrecognized uterine rupture, and the placental site. If the placenta is attached to the defective scar from a previous cesarean section, the bleeding may be furious and intractable; Slemons[8] advised hysterectomy in such instances.

Hemorrhage should be anticipated in every cesarean section. There should be a functioning venoclysis with a No. 18 gauge needle started before the anesthetic is begun. In addition to preoperative blood replacement there should be a unit of crossmatched blood available in the operating room for even the "routine" case. If the operation is done for antepartum hemorrhage or toxemia, spinal anesthesia should be avoided because of the inherent risk of hypotension. Loss of blood will be reduced if the surgeon uses local infiltration. The placental site should be spared the trauma of rough sponging and the suction tip. Blood will be saved and morbidity reduced if myomectomy is avoided. In event of intractable bleeding from profound atony, placenta praevia, abruptio with uteroplacental apoplexy, rupture or perforation (from "failed forceps"), hysterectomy may be necessary.

The author has observed two cases in which the patient underwent cesarean-hysterectomy and several hours after operation lapsed into severe shock from internal hemorrhage. The increased vascularity of the pelvic structures in the pregnant state makes cesarean-hysterectomy a formidable undertaking. All vascular pedicles should be doubly ligated, as the risk of a major vessel's retracting is considerable. A progressively falling volume of erythrocytes as determined by hematocrit is the best laboratory indication of internal hemorrhage. If the physician is convinced there is continuing bleeding it is mandatory that he reopen the abdomen. Total hysterectomy is fraught with special hazards in the pregnant state, and, like all surgical operations during gravidity, should be avoided unless really necessary. Bleeding from the vaginal cuff and internal hemorrhage from vascular pedicles are calculated risks from this operation.

490 Post Street.

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Discussion by DONALD W. DECARLE, M.D., *San Francisco*

To me, there is but one obstetrical complication in the presence of which I must, at times, admit to actual panic. That complication is postpartum hemorrhage. This is particularly true in the presence of bleeding which one can not only see but also hear. I have known men far more experienced than I to be so completely unnerved in its presence that clear, sound judgment is lost. It is the complication which must always be feared as long as it is potentially present at every delivery.

As a subject for discussion, it has, therefore, been wisely chosen. It can never be exhausted as long as it leads the list of fatal complications in the field of obstetrics. As Dr. Melody has pointed out, in order to combat postpartum hemorrhage, one must be conversant with every phase of the conditions underlying it. This necessitates routine and frequent rechecking of the blood throughout every pregnancy. Potential or actual anemia as distinguished from the physiological hydremia of pregnancy can be recognized and properly treated before the onset of labor only by such a method. I deem this most important, since it can mean the margin of difference between life and death in the event of postpartum hemorrhage. The practice of placing the patient on iron therapy without such a routine hemoglobin evaluation only creates a false sense of security. It should be severely condemned.

For the most part, I agree wholeheartedly with Dr. Melody. However, in the matter of handling the third stage of labor, I still feel that the Credé maneuver, when properly carried out, is a valuable procedure. If one's hand is on the fundus during the third stage, certainly there is far less chance of the uterus' filling with blood concealed behind an undelivered placenta. The same is true of the Credé maneuver when an oxytocic agent is employed at the onset of the third stage. Otherwise, the placenta may become incarcerated.

Dr. Melody has very definitely changed our way of thinking on at least two points. In the first place, employment of the Voorhees bag has been largely replaced by more modern procedures. The danger of introduction of toxic material into the uterine sinuses by the use of the uterine bag should lead to complete and universal discarding of this procedure. Secondly, the same holds true of our attitude toward the fetus which has died in utero. It is apparently much safer to empty the uterus as soon as a diagnosis of intrauterine death has been made.

Through the efforts of the essayist, a supply of Fraction I is now available at Children's Hospital in San Francisco. It was my recent misfortune to watch as a patient died of bleeding which could not be controlled even by hysterectomy. Had this material been available at the time, such an outcome might have been prevented.

CASE REPORT

The Transpalatal Approach for Juvenile Fibroma

WALTER E. HECK, M.D., and ROBERT C. MCNAUGHT, M.D.,
San Francisco

JUVENILE fibroma is a specific, highly vascular, non-infiltrating, essentially benign neoplasm[4] that occurs in the nasopharynx of pubescent persons, almost always males. The term "nasopharyngeal fibroma of adolescence" has also been used to describe such lesions, although the period of onset is just before puberty.

Other synonyms include juvenile nasopharyngeal fibroma, or angiofibroma; juvenile basal fibroma (basal referring to the basi-occipital site); bleeding fibroma of adolescence, and even fibroid of the nasopharynx.

INCIDENCE

Figi and Davis[2] reported the largest series of cases—114 observed in a 40-year period at the Mayo Clinic. Martin and co-workers[4] reported 29 cases in a 20-year period.

PATHOLOGY

A juvenile fibroma (Figure 1) is a smooth, bulky, red, non-ulcerated tumor in the nasopharynx, readily visible by direct anterior rhinoscopy or in a nasopharyngeal mirror. Figi[2] expressed the opinion that the appearance is so distinctive that a physician who is familiar with the tumor might make exception to the rule that biopsy of a tumor is imperative. It is doubted, however, that he would strongly advocate such a departure.

The stroma of the tumor, as microscopically observed, is made up of fibrocytes and contains many small blood vessels. As the vessels are characteristically lacking in musculature, they have no contractibility. This is one reason for the tendency of such tumors to bleed excessively. The covering epithelium is usually that of the area of origin. Often in the typical pseudostratified, ciliated, columnar epithelium (so-called respiratory or Schneiderian epithelium) there are areas of metaplasia to squamous epithelium, stratified or even pavement in type.

CLINICAL COURSE

The usual course observed clinically begins with the symptom of nasal obstruction in a pubescent or early adolescent person. (Obviously, the tumor must grow in size for a time before obstruction becomes symptomatic.) Rhinolalia clausa usually is observed. Then, typically, the patient begins to have nasal hemorrhages, usually severe and difficult to control. As the tumor grows it distends the adjacent structures of the nasopharynx and nose. The facial deformity has been termed "frog-face."

Often the history includes note of attempted biopsy, or of attempted "polypectomy" based on an erroneous diagnosis, which had to be terminated because of hemorrhage.

From the Division of Otolaryngology, Department of Surgery, Stanford University School of Medicine.

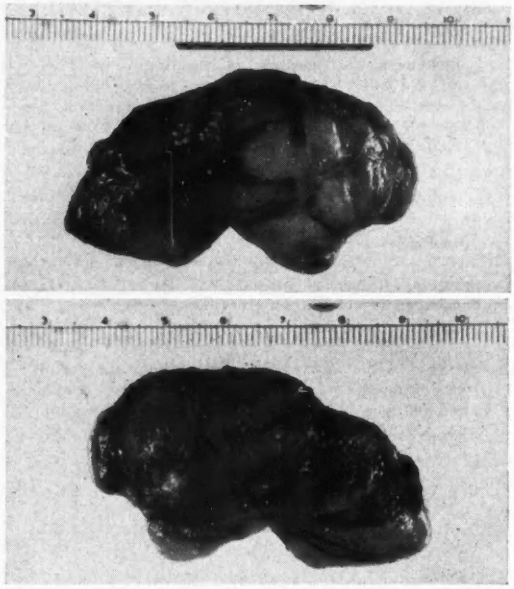

Fig. 1.—Photograph of juvenile fibroma removed from the second patient. *Upper*—the presenting (antero-inferior) surface. *Lower*—the base of the tumor.

At the time of full body growth, usually at 20 to 25 years of age, the tumor becomes smaller; but, as Figi[2] emphasized, the regression is not as pronounced as the literature implies.

PATHOGENESIS

The probable pathogenesis of these tumors is correlated with the clinical course. Up to the twentieth year the body of the sphenoid bone is joined to the basi-occiput (that part of the occipital bone anterior to the foramen magnum) by a plate of cartilage.[5] The juvenile fibroma is believed to arise from the perichondrium of this cartilaginous plate. After the twentieth year, ossific union takes place between the sphenoid bone and the basi-occiput, usually over a two- or three-year period. Any spontaneous regression of the tumor, therefore, occurs at this time.

REASONS FOR TREATMENT

There are four compelling reasons for vigorous therapy in the presence of this entity, the first of which is the repeated hemorrhages. They are very severe, often necessitating multiple transfusions, and are very difficult to control. The second is the mechanical obstruction of the nasopharynx and nasal fossae, which makes the patient subject to secondary infections of the sinuses and the middle ear. The third is the facial deformity which may be a permanent disfigurement once definitely established. Finally, cases are reported of encroachment on the orbit or even intracranial extension. The larger the tumor is permitted to grow, the more difficult its removal.

REPORT OF TWO CASES

CASE 1. The patient, an 11-year-old boy, first observed in the ear, nose and throat department of the Stanford Outpatient Clinic in 1947, gave a history of nasal obstruction and repeated epistaxis during the previous ten months. A diagnosis of nasal polyp had been made elsewhere and an attempt to excise a specimen for biopsy was followed by hemorrhage. The patient was then referred to the Stanford clinic. The diagnosis was made on the basis of biopsy, and the patient was first given external radiation therapy. In the ensuing two years, he had four interstitial insertions of radon seeds. In September 1949, surgical excision was carried out, with a preliminary left external carotid ligation. The approach was made by a longitudinal, transpalatal incision, after the technique of Brown.[1] The soft palate was incised at the midline, and the incision carried forward about one and one-half centimeters into the hard palate. The exposed part of the bony palate was removed. The tumor extended into the left parapharyngeal space. It compressed, but did not enter, the left antrum. The base of the tumor was pried loose by means of a periosteal elevator. The incision was closed and healed by primary intention. When the patient was last observed in the fall of 1950, there was no sign of persistent or recurrent tumor. The nasal, nasopharyngeal, and palatal structures were anatomically normal.

CASE 2. A 15-year-old boy first observed in December 1950 was referred for treatment of a typical juvenile fibroma. The history, results of examination, and microscopic appearance of biopsy specimens previously excised were characteristic. Without preliminary radiation or carotid ligation, the tumor was removed surgically. The approach was through a transverse transpalatal incision made about one and one-half centimeters anterior to the posterior edge of the hard palate, and the exposed palatal bone and adjacent area of nasal septum was removed. The tumor was pried loose at its base by means of a periosteal elevator. Bleeding from the site of origin was stopped by thorough electrocoagulation. The incision was closed and healed primarily except at the middle where there was sloughing at the site of a suture. A small dental prosthesis was fashioned to cover this defect, and, when the patient was last observed, six months postoperatively, the fistula had spontaneously closed. There was one small nodule of apparently persistent or recurrent tumor, and this was electrocoagulated in the out-patient clinic.

SURGICAL APPROACH

Figi[2] expressed the opinion that the best surgical approach to such tumors is transantrally, through the maxillary sinus by a Caldwell-Luc incision, with removal of the lateral wall of the nose. By this approach, excellent exposure is obtained, but it entails permanent disruption of nasal structure. In the two cases here reported, the transpalatal approach was adequate, and the anatomical disruption was less.

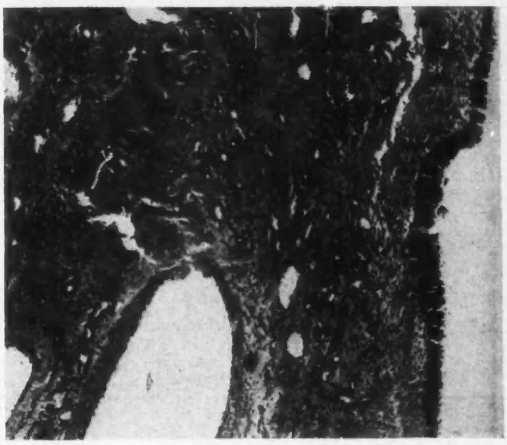

Fig. 2.—Microscopic appearance of the juvenile fibroma removed from the second patient, showing the respiratory epithelium, fibrous stroma, and the endothelial-lined capillaries and blood spaces.

OTHER THERAPY

The use of interstitial radiation in Case 1 and of surgical diathermy in Case 2 is in agreement with generally-used therapy of juvenile fibromas. Because the clinical course of the disease is related to the period of body growth, the question of using hormonal therapy is always raised. Kerwin[3] recently advocated the use of androgens, and reported one case in which that treatment was given. Hormonal therapy has been previously tried and discarded by others.

SUMMARY

A transpalatal approach was used in two cases for removal of juvenile fibroma. Exposure of the operative field was adequate and the tumors were apparently successfully excised. Postoperatively the structure was essentially normal, as contrasted with the anatomic disturbance remaining after use of the transantral approach.

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EDITORIAL

Malaria in Veterans Returning from Korea

The return of large numbers of Armed Forces personnel to the United States from Korea focuses attention, for the second time within a decade, on the age-old problem of malaria. Tertian malaria (P. vivax) is endemic in Korea, and numerous cases of malaria have been observed in these returning personnel. Since many of them have been taking suppressive therapy, the disease will frequently become clinically evident after discharge or while they are on leave in their home communities. The resulting problem is of national importance, and is twofold in nature: First, the recognition and treatment of the acute attack, and prevention of relapses, and secondly, the prevention of new foci of endemic malaria in areas where suitable insect vectors, certain species of Anopheles mosquitoes, are known to be present.

In the recognition of acute attacks the demonstration of parasitemia by means of blood smears is essential. In order that a record may be kept of all positive cases, so that appropriate sanitary and public health measures may be taken to protect the communities in which the possibility of endemic transmission exists, the Public Health Service has requested that all positive, doubtful, or controversial blood slides be referred, through the laboratories of the State Board of Health, to the National Depository for Malaria Slides, Parasitology Laboratories, Communicable Disease Center, P.O. Box 185, Chamblee, Ga., where all slides submitted will be reviewed by a group of experts and the results will be reported to the Health Department and to the patient's physician. Where indicated suitable sanitary measures will then be undertaken jointly by the State Health Department and the Public Health Service.

In the treatment of malaria considerable progress has been made since World War II. Newer antimalarial agents superior to the familiar quinine and atabrine have been developed, and many substances are at present under active investigation. The treatment of the acute attack is relatively simple. Chloroquine is superior in all respects to quinine and atabrine and is currently regarded as the drug of choice. The recommended dosage is 1 gm. orally followed by 0.5 gm. in six hours and 0.5 gm. daily for two days, a total of 2.5 gm. in three days. This regimen will abolish parasitemia and will usually stop acute attacks promptly, but has no significant effect on the tissue or exoerythrocytic forms of the parasite, the source of recurring parasitemia and relapses. To prevent relapses of vivax malaria the treatment program should combine an 8-amino quinoline, such as pentaquine, with quinine. Pentaquine is related to plasmochin but is considerably less toxic. The recommended dosage consists of 10 mg. of pentaquine base and 0.65 gr. of quinine sulfate orally every eight hours for 14 days. This combination has demonstrated effectiveness on the tissue forms and has significantly lowered the relapse rate of tertian malaria.

If the measures of early recognition, prompt reporting, and adequate treatment are carried out, it can be confidently expected that the development of new foci of malaria in the United States will be effectively prevented.

Letters to the Editor . . .

October 5, 1951

EDITOR,
CALIFORNIA MEDICINE:

I have received a beautiful display box of an antibiotic in the many useful dosage forms produced by the manufacturer.

I wish to record my thorough disapproval of drug houses sending samples and making display advertising to the medical profession. In as far as it is propaganda, the medical profession ought to have the courage to resist it. In as far as it is education, the medical profession ought to have pride enough to say, "We will manage our own education." The cost of this advertising either is returned to our own pockets through federal taxation, or else it is loaded onto our patients as reflected in the price they have to pay for the drugs we choose to order for them.

The first is foolish and the second is unconscionable. This protest is not made merely to hurt the feelings of the pharmaceutical companies but is a thoughtful step in a crusade that I have been waging in a desultory fashion for a long time without as yet having gained very many converts. The difficulty is of course aureogenic amblyopia.

R. R. NEWELL, M.D.
San Francisco

Endogenous Cholesterol

In 1933 it was shown by Schoenheimer and Breusch[1] that mice fed a cholesterol-free diet are able to synthesize cholesterol. Experimental evidence suggesting that this endogenous cholesterol is a more important factor than dietary cholesterol in the production of arteriosclerosis is currently reported by Siperstein[2] and associates of the University of California. The California biochemists based this conclusion on tests of the cholesterol-synthesizing power of arterial tissues.

Several 0.5 cm. segments of the aorta were removed from chickens and rabbits. Liver samples were taken as controls. Adopting methods previously perfected by Chernick,[3] each aortic segment was incubated for three hours in 5 cc. of Krebs-bicarbonate buffer solution containing 1 mg. of doubly C^{14}-labeled sodium acetate. At the end of three hours the CO_2 envolved was trapped in KOH and its C^{14} content determined. In typical examples an average of 5.1 arbitrary units of C^{14} content were recovered per gram of rabbit aortic tissue, with 13.5 C^{14} units recovered per gram in control tests with the liver. Analysis of the fluids in the flasks showed that on an average 36.5 arbitrary units of acetate-C^{14} were synthesized into cholesterol per gram of aortic tissue. About four times that amount was synthesized by each gram of liver.

Endogenous cholesterol as the dominant factor in the pathogenesis of arteriosclerosis is suggested by Chaikoff's[4] earlier demonstration that on a cholesterol-free diet chickens injected with stilbestrol develop hypercholesterolemia promptly and atherosclerosis in about a year.

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W. H. MANWARING, M.D.
Palo Alto

Bacterial Agglutinins in Cancer

It was noted by Parfentjev and Duran-Reynals[1] of Yale University that there is a fall in Proteus agglutinins in chicken serum throughout the development of Rous sarcoma. This led them to make a statistical study[2] of these agglutinins in human serums in malignant disease.

Selecting Proteus OX19 as their test organism, they found that in infants under one year of age, only one out of fourteen had demonstrable Proteus agglutinins. This increased to three out of ten by the fifth year. Among normal adults 95 per cent had these agglutinins. Among 163 hospital patients with non-malignant disease 130, or 80 per cent, had Proteus agglutinins. Of 28 patients with cancer, only eight, or 28 per cent, had the agglutinins. Among 14 patients successfully treated for cancer with no evidence of recurrences, 12, or 86 per cent, were agglutinin-positive. A similar paucity of bacterial agglutinins was previously reported by other investigators[3] in both Hodgkin's disease and leukemia.

Since Proteus agglutinins are present in the globulin fraction of human serum, the Yale University clinicians concluded that the subnormal titer in untreated cancer patients may be due to a quantitative or qualitative abnormality in serum globulins.

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W. H. MANWARING, M.D.
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Council Meeting Minutes

Tentative Draft: Minutes of the 386th Meeting of the Council, San Francisco, November 11, 1951.

The meeting was called to order by Chairman Shipman in Room 220, St. Francis Hotel, San Francisco, at 9:30 a.m., Sunday, November 11, 1951.

Roll Call:

Present were President MacLean; Speaker Charnock; Councilors Shipman, Lum, West, Ball, Loos, Morrison, Dau, Ray, Green, Pollock, Frees, Thompson, Bailey, Varden and Heron; Secretary Daniels.

Absent for cause: President-elect Alesen, Councilors Sampson and Montgomery, Editor Wilbur.

A quorum present and acting.

Present by invitation were Vice-Speaker Randel, Executive Secretary Hunton, Assistant Executive Secretary Thomas, Legal Counsel Hassard, Messrs. Clancy, Gillette and Pettis of public relations staff, Mr. Ben H. Read of the Public Health League of California; county society executive secretaries William Nute of San Diego, Robert Wood of San Mateo; Dr. D. H. Murray, legislative chairman.

Present during all or part of the meeting: Dr. Malcolm Merrill, acting State Director of Public Health; Dr. John R. Upton, Blood Bank Commission chairman; Dr. Francis Hodges, secretary of California Physicians' Service; Dr. Alson Kilgore; and Messrs. Clem Whitaker, Jr., and Ned Burman of public relations counsel.

1. *Minutes for Approval:*

(a) On motion duly made and seconded, minutes of the 385th Council meeting, held September 22, 1951, were approved.

(b) On motion duly made and seconded, minutes of the 229th Executive Committee meeting, held October 25, 1951, were approved.

2. *Membership:*

(a) A report of membership as of November 9, 1951, was received and ordered filed.

(b) On motion duly made and seconded, three 1950 members whose dues had been received were voted reinstatement.

(c) On motion duly made and seconded, 39 members (1951) whose dues had been received were voted reinstatement.

(d) On motion duly made and seconded in each instance, nine applicants were voted Associate Membership. These were:

Rosemary O. Brunetti, Theodore Carlton, and Isamu Nieda, Alameda-Contra Costa; Margaret J. Miller, Russel F. Rypins, and Wilfred Toreson, San Francisco; Edward T. Jewett, San Mateo; Salvador Jacobs and Joseph D. Warrick, Ventura.

(e) On motion duly made and seconded in each instance, four applicants were voted Retired Membership. These were:

Peter Joseph Cuneo, Kern County; George O. Chalfant, San Francisco County; Jess F. Jacobsen, San Francisco County; William Carston Lynch, San Mateo County.

(f) On motion duly made and seconded in each instance, reductions of dues were voted for four applicants because of illness or postgraduate study.

3. *Financial:*

(a) A report of bank balances as of November 9, 1951, was received and ordered filed.

(b) A report of income and expenditures for October and for the four months ended October 31, 1951, was received and ordered filed.

4. *California Physicians' Service:*

Dr. Francis T. Hodges, Secretary of C.P.S., reported that as of October 28, 1951, there were 10,928 physician members and approximately 908,000 beneficiary members. He expressed the expectation that not later than the start of 1952, and possibly earlier, full payment on the present fee schedule will be made.

5. *State Department of Public Health:*

Dr. Malcolm Merrill, Acting State Director of Public Health, reported on medical screening being given Mexican nationals who are admitted to the state as agricultural or other workers. It is hoped to improve the medical screening in Mexico through the use of state representatives working in Mexican cities.

Dr. Merrill also reported that 184 cases of malaria have been reported in California to date, mostly late cases contracted and suppressed in the early stages in Korea. He also stated that the department is working with medical school deans and others in establishing regulations for laboratories which seek licenses to use animals. The State Board of Health is also planning hearings on proposed regulations under the Clinical Laboratory Act.

Dr. Merrill reported that Dr. Wilton L. Halverson, State Director of Public Health, had been elected

President of the American Public Health Association and on motion duly made and seconded it was voted to send Dr. Halverson the sincere congratulations of the Association on this honor.

6. *C.P.S. Fee Schedule Committee:*

A report by Dr. DeWitt Burnham, chairman of the C.P.S. Fee Schedule Committee, was read. It showed that a subcommittee of eight members had been appointed, that questionnaires had been sent to all physician members and some 3,000 replies received to date. The replies will be mechanically tabulated and the committee will meet one week hence to study the ranges of fees shown in these replies.

7. *C.P.S. Study Committee:*

Dr. Wilbur Bailey, chairman of the C.P.S. Study Committee, reported on the initial meeting of the committee, at which it was tentatively decided to engage in market surveys and other business studies designed to produce factual information. He presented two cost estimates for such studies, total costs running about $30,000 to $40,000.

Dr. Alson Kilgore, a member of the committee, discussed the possible future courses for C.P.S. and suggested that the House of Delegates first determine which course should be taken; once that is determined, the committee could seek authorization to continue its studies.

On motion duly made and seconded, it was voted that the Council discuss C.P.S. affairs in the report of the Council to be made to the House of Delegates and to request that the House of Delegates approve the appropriation of funds to make factual business studies of C.P.S. and other medical cost prepayment plans.

8. *Committee on Industrial Accident Commission:*

Dr. Frank J. Cox, chairman of the Committee on Industrial Accident Commission, requested a determination of whether his committee should seek a fee schedule based on fee for service, on flat fees or on some combination of the two. He reported that his committee is about to receive factual data on some 10,000 industrial injury cases, from which it can accurately predict the effect on compensation insurance premiums of an increase in medical costs. It is now believed that sufficient data have been assembled to warrant request for a flat 25 per cent increase in fees.

On motion duly made and seconded, it was voted to recommend that the committee seek a fee-for-service fee schedule and request a percentage increase in fees justified by the factual material developed.

9. *Blood Bank Commission:*

Dr. John R. Upton, chairman of the Blood Bank Commission, reported that ten blood banks are now either operating or forming in the statewide system and that eight are in the armed forces blood procurement program. He also reported on his participation in the Minneapolis meeting of the American Association of Blood Banks and on exhibits given by the commission at several recent medical meetings.

On motion duly made and seconded, the Council expressed a vote of confidence in the Blood Bank Commission and in its chairman, Dr. Upton.

10. *Blood Bank of San Bernardino-Riverside Counties:*

On motion duly made and seconded, it was voted to permit the Blood Bank of San Bernardino-Riverside Counties to complete payment on its first $10,000 loan before starting repayment of the second $10,000 advance.

11. *Governor's Conference on Problems of the Aging:*

Dr. Edwin L. Bruck reported on the Governor's Conference on Problems of the Aging, held in Sacramento on October 15-16, 1951, and stated that a complete report was under preparation for publication after the first of next year. This will contain summaries of all decisions reached.

12. *Public Policy and Legislation:*

Dr. Dwight H. Murray, legislative chairman, reported on several national legislative items and discussed the need of supporting the American Medical Education Foundation. He reported that "$100 a year" or "$10 a month" clubs are being formed among physicians in various states to aid this fund and stressed the importance of aiding such groups.

Discussion was held on recent statements by Governor Warren on the subject of compulsory health insurance.

13. *Legal Department:*

Mr. Hassard discussed the pending litigation in San Diego and reported on action taken by the State Commissioner of Insurance against two underwriters of health insurance programs.

14. *Committee on Emergency Medical Service:*

On motion duly made and seconded, approval was voted a manual on the care of emergency cases drafted by state civil defense authorities and previously approved by Dr. Justin J. Stein, chairman of the Committee on Emergency Medical Service.

15. *Advisory Planning Committee:*

On motion duly made and seconded, Mr. William Nute, executive secretary of the San Diego County Medical Society, was elected a member of the advisory Planning Committee.

Mr. Hunton discussed the plans made for securing a test distribution of a plaque designed by the public relations department of the A.M.A. for display in physicians' offices.

16. *San Francisco Medical Society:*

On motion duly made and seconded, it was voted to express a reasonable interest in the possibility of the Association's occupying space in a medical center building tentatively planned for construction by the San Francisco Medical Society.

17. *California Mineral Springs:*

On motion duly made and seconded, the suggestion of a member for a more active part in the de-

velopment of mineral springs resorts in California was voted to be referred to the Committee on Hospitals, Dispensaries and Clinics.

18. *Interim Session of House of Delegates:*

(a) On motion duly made and seconded, it was voted to prepare an amendment to Article V, Section 2 of the By-Laws to clarify the representation of county societies in the House of Delegates.

(b) On motion duly made and seconded, it was voted to prepare suitable amendments to make the Vice-Speaker of the House of Delegates a member of the Council.

(c) On motion duly made and seconded, it was voted to request the Committee on Scientific Work to prepare a suitable scientific program for the December 1-2 session.

19. *Practical Nursing:*

A request for cooperation from a group of practical nurses was received and ordered referred to the committee composed of Drs. Howard Naffziger, Dwight L. Wilbur and Arthur Kirchner.

20. *Public Relations:*

Mr. Clem Whitaker, Jr., public relations counsel, urged that members of the Woman's Auxiliary participate in women's organizations throughout the state.

21. *California State Department of Education:*

On motion duly made and seconded, it was voted to recommend Dr. Ulrich A. Fritschi of Sacramento for appointment on an advisory board on school health problems to be established by the State Department of Education.

22. *Time and Place of Next Meeting:*

It was decided to leave the time and place of the next meeting to the call of the chairman, with the exception that a meeting would be held during the December 1-2, 1951, period in Los Angeles.

23. *C.M.A.-C.P.S. Liaison Committee:*

A report from the C.M.A.-C.P.S. Liaison Committee was read and on motion duly made and seconded it was voted to approve a contract between C.P.S. and the Old Sailors' Home.

Adjournment:

There being no further business to come before it, the meeting was adjourned at 4:40 p.m.

SIDNEY J. SHIPMAN, M.D., *Chairman*
ALBERT C. DANIELS, M.D., *Secretary*

In Memoriam

BONYNGE, CHARLES W. Died in Los Angeles, October 6, 1951, aged 71, of ruptured abdominal aneurysm. Graduate of the University of Southern California School of Medicine, Los Angeles, 1903. Licensed in California in 1904. Doctor Bonynge was a member of the Los Angeles County Medical Association, a life member of the California Medical Association, and a Fellow of the American Medical Association.

✤

CHRISTESON, EDGAR L. Died in Los Angeles, September 25, 1951, aged 59, of carcinoma of the duodenum. Graduate of the St. Louis University School of Medicine, 1922. Licensed in California in 1930. Doctor Christeson was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

COOK, ORRIN S. Died in Sacramento, October 24, 1951, aged 59. Graduate of the University of California Medical School, Berkeley-San Francisco, 1917. Licensed in California in 1917. Doctor Cook was a member of the Sacramento Society for Medical Improvement, the California Medical Association, and a Fellow of the American Medical Association.

✤

CUMMINS, HARVEY R. Died in Los Angeles, September 18, 1951, aged 43. Graduate of the Emory University School of Medicine, Emory University, Georgia, 1934. Licensed in California in 1945. Doctor Cummins was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

DOUGHERTY, JOHN A. Died in Piedmont, October 6, 1951, aged 60, after a long illness. Graduate of Vanderbilt University School of Medicine, Nashville, 1916. Licensed in California in 1923. Doctor Dougherty was a member of the Alameda-Contra Costa Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

GALBRAITH, ALEXANDER. Died in Oakland, October 13, 1951, aged 80. Graduate of Rush Medical College, Chicago, 1899. Licensed in California in 1904. Doctor Galbraith was a retired member of the Alameda-Contra Costa Medical Association, and the California Medical Association, and an Associate Fellow of the American Medical Association.

✤

JONES, GEORGE W. Died in Pomona, October 8, 1951, aged 51, of coronary artery disease. Graduate of University of Cincinnati College of Medicine, 1925. Licensed in California in 1940. Doctor Jones was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

LONG, FREDERICK. Died in San Francisco, October 19, 1951, aged 68. Graduate of the University of California Medical School, Berkeley-San Francisco, 1910. Licensed in California in 1910. Doctor Long was a member of the San Francisco Medical Association, the California Medical Association, and the American Medical Association.

✤

LONG, JAMES H. Died in Pasadena, June 30, 1951, aged 71, of coronary thrombosis. Graduate of Harvard Medical School, Boston, 1914. Licensed in California in 1925. Doctor Long was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

Questions and Answers about C. P. S.

Question: **Does a woman lose her maternity benefits immediately if she transfers from a group enrollment to the direct payment program?**

Answer: No, not immediately. The $50 allowance toward the physician's fee for normal maternity care is continued for nine months after the date of transfer to direct payment membership.

Question: **In treating veterans under the Home Town Care Program, how do I obtain authorization for additional services which become necessary and which are in excess of what has been originally authorized for the period?**

Answer: If in the course of treating a veteran patient it becomes evident that services in addition to those already authorized are necessary, the physician should telephone collect to the Medical Authorization Officer in the nearest Regional Office of the Veterans Administration—San Francisco, Los Angeles or San Diego.

Question: **The new C.P.S. medical contract limits x-ray and laboratory services outside the hospital to $25 and $10 respectively per contract year. How may the physician know if the patient has used all or any part of these allowances?**

Answer: Whenever a physician member who performs x-ray and laboratory services in his own office submits a bill to C.P.S. for such services, he is sent a form which indicates (1) the amount which will be paid by C.P.S.; (2) the amount of the $25 and $10 allowances which remain. The form also indicates if the allowances have already been exhausted and the date when they will be renewed for another year.

Question: **How does the physician bill for x-ray and laboratory services rendered to a C.P.S. patient (who is under the income ceiling) after the yearly $25 and $10 allowances for each have been exhausted?**

Answer: In these instances, the physician should bill the patient directly. C.P.S. members are responsible themselves for all services which are beyond the provisions of their C.P.S. coverage, and the income clause does not apply when C.P.S. coverage does not apply.

Question: **What part does the physician have in filling out the hospital admission notice when one of his C.P.S. patients enters the hospital?**

Answer: The physician's part in connection with the hospital admission notice is indispensable to action by C.P.S., because, among other things, it gives the diagnosis. This information, which only the physician can provide, is absolutely essential to C.P.S. Without it, C.P.S. cannot determine its liability in the case, based on the contract held by the patient. If the physician does not fill in this information himself, he should authorize a member of the hospital's staff to do it for him.

Question: **Under the revised C.P.S. direct payment program which does not provide out-patient medical services, what happens if a patient is receiving medical care at the time of transfer from group membership to direct pay?**

Answer: When a C.P.S. member is receiving medical care under the two-visit-deductible medical contract at the time of transfer to the direct payment program, the terms of the two-visit-deductible contract are continued until the benefits for the condition being treated have been exhausted.

Question: **I treated a veteran patient until his condition indicated that further treatment at the time was unnecessary. A few months later the veteran complained of a recurrence of the condition and requested more treatment. What is the simplest method of obtaining authorization under these circumstances?**

Answer: Inasmuch as the veteran had already been authorized by the Veterans Administration for treatment of the condition, it is not necessary to follow the normal procedure in obtaining authorization. Instead, the physician may contact the nearest VA Regional Office by telephone or telegram, collect. Telephone numbers are: San Francisco, YUkon 6-3500, extension 370 or 372; Los Angeles, PRospect 4711, extension 701; San Diego, FRanklin 9-8031.

Question: **As regards retroactive payment by the Veterans Administration for services not previously authorized, is there any difference in the regulations which apply to Spanish-American War veterans and other veterans?**

Answer: Yes. The regulation applying to Spanish-American War veterans is: To be payable by the Veterans Administration, all services in each and every specific medical condition must be authorized in advance of the services being rendered.

Eligible veterans of other wars who require prompt treatment may receive it immediately (prior to authorization) if notification that the services have been rendered is sent to the C.P.S. Veterans program immediately afterward.

Question: **Do C.P.S. members enrolled under the individual family plan have any medical benefits; or, if not, can they extend their coverage to include medical benefits?**

Answer: The standard coverage provided by the individual family plan is surgical and hospital. However, members enrolled under this plan have the option of subscribing for medical-services-while-

hospitalized benefits by paying the additional cost over rates for the standard coverage. All eligible family members must subscribe for this additional coverage in order for any one of them to obtain it. Out-patient medical coverage (the two-visit-deductible medical contract) is not available to individual family plan members. In addition, their surgical contract provides for surgery and treatment of fractures and dislocations and x-rays to determine same *in the doctor's office.*

Change in Method of Authorization for Home-Town Care of Veterans

Effective November 1, an important change was made by the Veterans Administration in the method for eligible veterans to receive authorization for outpatient medical treatment.

Henceforth, veterans seeking care on an outpatient basis, either at a VA clinic or from a private physician under the C.P.S.-VA Home Town Care Program, must make application, in writing, directly to the VA regional office in San Francisco, Los Angeles or San Diego. Formerly, applications could be made either through the VA or through a private physician.

Except in cases requiring prompt treatment, the change makes it unnecessary for physicians to complete Form 52 (the "request for authority for treatment"). C.P.S. will send the authorization to the physician of the veteran's choice after the veteran's application has been approved by VA.

In cases where prompt treatment is indicated, the veteran may apply directly to a private physician. In such instances the physician should request authorization by submitting a Form 52 immediately to C.P.S.

Physicians may contact the nearest VA regional office by telephone or telegraph, collect, if any additional services are needed which have not been authorized.

(Note: C.P.S. has mailed a new instruction manual to each physician member who is treating veterans under the Home Town Care Program. Manuals will also be sent, on request, to any physician member not now treating veterans who desires to participate in the program in the future.)

C. P. S. Green Envelopes Misused

Many physicians apparently are misunderstanding the use which was intended for the special green envelopes recently supplied by C.P.S. to doctors' offices, the health plan reports.

The green envelopes, marked for the attention of the Medical Director, were devised to speed C.P.S. handling of bills for complicated or unusual services rendered to C.P.S. patients. Although such bills customarily are brought to the attention of the Medical Director, a saving of time results from having them sent directly to the Medical Director — instead of having them routed through the normal processing channels as is done with routine bills.

Early experience, however, indicates that much of the good results to be achieved by use of the envelopes is being lost because, in many instances, they are being used for routine bills.

In addition, C.P.S. points out, when a bill is sent in a green envelope it should be accompanied by a short report from the physician, describing the unusual or complicated aspect of the case.

NEWS and NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

At the November election the following officers of the Los **Angeles Radiological Society** for the coming year were elected: President, Harold P. Tompkins, M.D., Los Angeles; vice-president, Richard L. Smith, M.D., Santa Monica; secretary, John B. Hamilton, M.D., Glendale; treasurer, M. M. Haskell, M.D., Long Beach.

* * *

The first day of the annual mid-winter meeting of the **California Society of Pathologists,** held December 1 and 2, in Los Angeles, was dedicated to Dr. Ernest M. Hall, retiring professor of pathology of the School of Medicine, University of Southern California. As a tribute to Dr. Hall, the majority of the scientific contributions of the day were offered by former students and associates. Guest speakers included Dr. Stanley P. Reimann, professor of oncology and director of the Institute for Cancer Research, Philadelphia; Dr. Sidney C. Madden, professor of pathology at the School of Medicine, U.C.L.A.; and Dr. Riojun Kinosita, visiting professor of pathology, U.C.L.A., and professor of pathology at Osaka Imperial University.

* * *

Among grants totalling $160,756 in aid of research and training made last month by **United Cerebral Palsy** was one of $10,000 to support a study by Dr. H. W. Magoun, professor of anatomy, University of California, Los Angeles, on the physiology of the cerebral cortex and basal ganglia in relation to cerebral palsy.

SAN BERNARDINO

The Second Annual Regional **Medical and Surgical Institute** for the Southern California Counties, sponsored by the Postgraduate Activities Committee of the California Medical Association, is to be held at Arrowhead Springs Hotel, San Bernardino, January 17 and 18, 1952. Local arrangements will be under the direction of the Postgraduate Study Committee of the San Bernardino County Medical Society. The teaching staff will be furnished by the Medical Extension Division, School of Medicine, University of California at Los Angeles, and the program which has been planned by the Regional Postgraduate Study Committee representing the counties of San Bernardino, Orange, Riverside, Imperial and parts of San Diego and Los Angeles is as follows:

THURSDAY, JANUARY 17

8:00-9:00 a.m.: Registration, Arrowhead Springs Hotel

Morning Session

Chairman, R. C. Pollock, M.D., San Bernardino

9:30-10:30 a.m.—Recent Progress Related to Antibiotics—William L. Hewitt, M.D., assistant professor of medicine, University of California School of Medicine, Los Angeles.

10:30-11:30 a.m.—Toxemia of Pregnancy—Daniel G. Morton, M.D., chairman, department of obstetrics and gynecology, University of California School of Medicine, Los Angeles.

11:30-12:30 a.m.—Diagnosis and Treatment of Infections of the Hand—William P. Longmire, Jr., M.D., professor and chairman, department of surgery, University of California School of Medicine, Los Angeles.

12:30-2:00 p.m.—*Luncheon and Round Table*—Chairman, Arthur J. Nies, M.D., Orange.

Afternoon Session

Chairman, Delbert Williams, M.D., San Bernardino

2:00-3:00 p.m.—The Chemotherapy of Gastrointestinal Infections—William L. Hewitt, M.D.

3:00-4:00 p.m.—Office Gynecological Procedures (including Fundal and Cervical Cancer)—Daniel G. Morton, M.D.

4:00-5:00 p.m.—Diagnosis and Treatment of Lesions of Pancreas—William P. Longmire, Jr., M.D.

6:30 p.m.—*Dinner Meeting*—Chairman, Roger Vargas, M.D., San Bernardino.

Speaker—Stafford L. Warren, M.D., dean and professor of biophysics, University of California at Los Angeles.

FRIDAY, JANUARY 18

Morning Session

Chairman, Max Goodman, M.D., San Bernardino

9:00-10:00 a.m.—Clinical Use of Cortisone and ACTH—Roger O. Egeberg, M.D., chief of medical service, Wadsworth General Hospital, Veterans Administration Center, Los Angeles.

10:00-11:00 a.m.—Treatment of Head Injuries—John B. French, M.D., chief, neurosurgery and acting chief, neuropsychiatry, Veterans Administration Hospital, Long Beach.

11:00-12:00 noon—Use of Blood Fractions in Children—John M. Adams, M.D., professor and chairman of the pediatrics department, School of Medicine, University of California at Los Angeles.

12:15-1:45 p.m.—*Luncheon, Round Table Discussion*—Chairman, H. C. Barron, M.D., Riverside.

Afternoon Session

Chairman, Jack R. Bostwick, M.D., Brawley

2:00-3:00 p.m.—Emergency Neurosurgical Procedure—John B. French, M.D.

3:00-4:00 p.m.—Acute Respiratory Diseases—John M. Adams, M.D.

4:00-5:00 p.m.—The Diagnosis and Treatment of Thyroid Disease—Roger O. Egeberg, M.D.

SAN FRANCISCO

The Stanford University School of Medicine will offer the annual **postgraduate conference in clinical ophthalmology** from March 24 through March 28, 1952. The program this year will be devoted to ophthalmic surgery. Registration will be open to physicians who limit their practice to the treatment of diseases of the eye or eye, ear, nose and throat. In order to allow free discussion by members of the conference, registration will be limited to 30 physicians.

Instructors will be Dr. A. Edward Maumenee, Dr. Dohr-

mann K. Pischel, Dr. Jerome W. Bettman, Dr. Max Fine, Dr. Earle H. McBain, and Dr. Arthur J. Jampolsky.

Programs and further information may be obtained from the office of the dean, Stanford University School of Medicine, 2398 Sacramento Street, San Francisco 15, California.

* * *

Dr. Frederick C. Cordes, San Francisco, was named president-elect of the American Academy of Ophthalmology and Otolaryngology, October 18 at the annual session in the Palmer House, Chicago. Presidents of the Academy are elected a year in advance and take office on January 1 following the annual meeting. The incoming president will be Dr. James Milton Robb, Detroit, who will assume the office on January 1, 1952; Dr. Cordes will become president on January 1, 1953.

SANTA BARBARA

Physicians from the counties of Santa Cruz, Monterey, San Benito, San Luis Obispo, Ventura and Santa Barbara attended the Second Annual **West Coast Counties Regional Medical and Surgical Institute,** which was held at Cottage Hospital, Santa Barbara, October 25 and 26. The teaching program was arranged by the Regional Postgraduate Study Committee of the West Coast Counties in conference with Dr. Gordon E. Goodhart, associate director of medical extension education, University of Southern California School of Medicine, Los Angeles.

Transportation to points of interest in Santa Barbara and a tea in the afternoon on the first day were arranged by the Santa Barbara Auxiliary for the entertainment of visiting wives of physicians.

GENERAL

The Foundation of the American Society of Plastic and Reconstructive Surgery announced the winners of this year's awards in its competitive essay, at the annual meeting of the society in Colorado Springs, October 30 to November 1. They were: Dr. Richard B. Stark, New York City, a scholarship award for his essay, "The Cross-Leg Flap Procedure"; **Dr. Kathryn Lyle Stephenson,** Santa Barbara, California, honorable mention for "The Production of Ectopic Cartilage"; Dr. Michael N. Tempest, Leeds, Yorkshire, England, honorable mention for "Cross-Finger Flaps in the Treatment of Injuries to the Finger Tip"; and **Dr. Allyn J. McDowell,** North Hollywood, California, honorable mention for "Mass Treatment of Burns in Atomic Warfare."

Particulars pertaining to the 1952 essay competition may be had from the award committee, in care of Jacques W. Maliniac, M.D., 11 East 68th Street, New York 21, N.Y.

* * *

The Fifth American **Congress on Obstetrics and Gynecology** will be held in Cincinnati, Ohio, March 31 through April 4, 1952, at the Netherland Plaza Hotel. The congress will feature a comprehensive five-day scientific program, sponsored by the American Committee on Maternal Welfare, covering the medical, nursing and public health aspects of the maternal care team.

Further information can be obtained by writing to Mr. Donald F. Richardson, executive secretary, American Committee on Maternal Welfare, 116 South Michigan, Chicago 3, Illinois.

* * *

Dr. Wilton Halverson, director of the California State Department of Public Health, was elected president-elect of the American Public Health Association at the recent meeting of that organization in San Francisco. Dr. Halverson is at present on leave from his California office while making a special survey of health in South and Central America for the U.S. Public Health Service.

Dr. Gaylord W. Anderson of the University of Minnesota was installed as president of the A.P.H.A. at the meeting, to succeed Dr. William P. Shepard of San Francisco.

BOOK REVIEWS

POISONS—Their Isolation and Identification. By Frank Bamford, B.Sc., Late Director of the Medico-Legal Laboratory, Cairo. Third Edition, revised by C. P. Stewart, D.Sc., Ph.D., Reader in Clinical Chemistry, University of Edinburgh. 23 illustrations. The Blakiston Company, Philadelphia, 1951. 316 pages. $5.50.

As is indicated in the above title, this book has been revised by Dr. C. P. Stewart, who is toxicologist at the University of Edinburgh. Frank Bamford had had a very extensive experience as director of the medico-legal laboratory of the Government of Egypt, in Cairo, and his first edition of this book commanded immediate attention of toxicologists because of the clarity and completeness of the qualitative chemical procedures which he described for the isolation and identification of poisons. In this third edition, Dr. Stewart has kept the spirit of Bamford's previous two editions, and has added important recent information. Short-cuts are described, many pieces of laboratory equipment are described and illustrated with clear cuts, and the interpretation of symptoms for purposes of gaining clues which will guide the chemist in his search for the poison is especially helpful to the beginner. The book is intended only as a manual for the chemical laboratory and does not pretend to yield information concerning the clinical phases of toxicology, such as early diagnosis and treatment of cases of poisoning. Although it is a very satisfactory guide to the qualitative identification of poisons, there are few aids to the quantitative estimation of the amount of the poison present, except for alcohol, arsenic, lead, bismuth, borate, fluorine and zinc, and for an inadequate quantitative test for barbiturates. Another defect in the book is the amount of space devoted to general statements, especially concerning the toxic agents contained in many plants which are rarely the cause of poisoning, yet without specific tests which would be of aid in the identification of these poisons.

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AN ATLAS OF ANATOMY—Third Edition. By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S. (Edin.), Professor of Anatomy in the University of Toronto. **By Regions—Upper limb, abdomen, perineum, pelvis, lower limb, vertebrae, vertebral column, thorax, head and neck, cranial nerves and dermatomes.** The Williams and Wilkins Company, Baltimore, 1951. 657 pages (637 pages of figures and 20 pages of index). $12.00.

The passage of Grant's *An Atlas of Anatomy* into its third edition during the short space of some eight years is testimony to its general popularity and usefulness. The wide and ready acceptance of the work by student and practitioner alike is doubtless due to the emphasis given to the salient and important, rather than to an exhaustive treatment. Here the student finds not only illustrations of significant features of anatomy but their interpretation as provided by an experienced teacher.

The new edition is larger by some 70 new illustrations with improvement or replacement of many of the old figures. Of the new additions, the most noteworthy are the figures systematically revealing the arrangement of structures in the female pelvis and perineum, the new advances in the designation of the pulmobronchial segments, and the recent modifications of the dermatome patterns as derived from the clinical and experimental work of Keegan. These many additions have mended earlier deficiencies and immeasurably added to the value of the atlas to place it among the best available. Of deficiencies which still remain, there are two: First, there is little on the variations in division of the recurrent laryngeal nerve which is so important to surgery of the thyroid gland; second, the absence of roentgenograms which, for instance, are far superior in revealing the epiphyses of bones in the manner in which the student usually observes them.

A word should also be said on the great improvement in the reproduction of the illustrations. In earlier editions these were somewhat flat, lacking in contrast and brilliance. The sharpening up of the figures has done much for their clarity and they have gained in the third dimension.

In short, Grant's *Atlas* has gone from strength to strength showing advance with every edition to place it in the forepart of works of this nature. Student and practicing physician could make no better selection for their studies.

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THE MANAGEMENT OF FRACTURES, DISLOCATIONS, AND SPRAINS—Fifth Edition. By John Albert Key, B.S., M.D., Clinical Professor of Orthopedic Surgery, Washington University School of Medicine; and H. Earle Conwell, M.D., F.A.C.S., Associate Professor of Orthopedic Surgery, University of Alabama School of Medicine. The C. V. Mosby Company, St. Louis, 1951. 1232 pages. $16.00.

This is one of the old standard American texts dealing with fractures, dislocations and sprains. It has been the standard work since 1934. The general formation of the text remains the same. It is profusely and well illustrated. The text is excellent in a general sense and the principles advocated are the result of extensive experience of the authors.

The composite ideas and experience of the two authors, it is an excellent text for anyone having to do with treatment of injuries of this type. Quite properly, the book tends toward conservatism. By following the directions and advice of this text in the care of injuries of the musculoskeletal system, certainly many unnecessary complications can be avoided.

The section on compound injuries is excellent. There is little emphasis on prophylactic antibiotic therapy. For example, the use of sulfa drugs locally to prevent infection is advised; no comment is made upon any of the newer antibiotics which have been developed during the past four years. There is, perhaps, not enough emphasis on the drainage of compound wounds in the management of compound injuries. The over-all discussion of principle, however, is excellent and bears careful study.

The various fractures occurring in the musculoskeletal system are covered adequately and completely with instructive illustrations. There can be no criticism of any portion of this book in that respect.

The section having to do with fractures of the forearm and elbow region emphasizes conservative management. The operative procedures illustrated, however, use either wire loops or the onlay plate and screw fixation principle. No mention is made of the use of intramedullary pin fixation for problems of this type. Apparently the only areas in which intramedullary nail fixation is advocated are in the tibial shaft and femoral shaft.

In the section on fractures of the hand, there is perhaps a bit too much emphasis on the use of traction and not quite enough on the maintenance of function. In inexperienced hands, a banjo-splint or a skeletal traction apparatus applied to an injured digit can lead to irreparable damage unless the principle of functional movement during the course of healing is followed through. The use of splints of this type predisposes to treating fractures of the hand on the basis of x-ray appearance instead of evaluation of the functional range of movement as an end result.

Generally, the section on injuries of the hip joint is excellent, but that portion having to do with fractures of the posterior acetabulum margin associated with dislocation of the hip does not mention immediate operation and reconstruction of the acetabular margin as a primary procedure. Conservative management of this type of injury has produced rather poor results in most instances. The results with reconstruction have been better. That part of the text dealing with treatment of the classical types of fracture of the hip is outstanding.

Always one of the classical portions of this book, the section on fractures of the shaft of the femur still is probably one of the major attractions. The same can be said for the section on fractures of the tibia and fibula.

In the discussion of fractures of the ankle area conservatism is stressed perhaps a bit more intensely than is necessary. There are certain positive indications for open repair of ankle joint injuries and these indications are not as clearly delineated as they should be.

Emphasis is laid upon the use of traction in the treatment of os calcis injury. There is a growing trend away from the use of this method generally.

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METABOLIC METHODS—Clinical Procedures in the Study of Metabolic Functions. By C. Frank Consolazio, Chief of Biochemistry, United States Army, Medical Nutrition Laboratory, Chicago, Ill.; Robert E. Johnson, M.D., D.Phil. (Oxford), Professor and Head of the Department of Physiology, University of Illinois, Urbana, Illinois; and Evelyn Marek, M.A., Biochemist, United States Army Medical Nutrition Laboratory, Chicago, Illinois. The C. V. Mosby Company, St. Louis, 1951. 471 pages. $6.75.

This valuable book is essentially a reprint of the U. S. Army "Report of a Manual of Metabolic Methods" by the same authors. Only very slight changes in textual material have been made, such as the addition of two or three new procedures. Changes in the excellent illustrations of apparatus, diagrams, and alignment charts for calculations are also negligible. A section on preservation of animal tissues in the field for histological studies has been added, and the useful tables on the normal ranges of the composition of body fluids have been revised and enlarged. The principal improvement is the inclusion of a fairly extensive bibliography (through 1949), arranged by subject matter.

The book presents in detail a large number of procedures for conducting metabolic studies. Collection and storage of specimens and the use of spectrophotometers, fluorometers, and flame photometers are well discussed. Sections on microbiological methods, physiological measurements, and studies in the field are included. The treatment of techniques for metabolic wards and of clinical laboratory procedure such as tolerance and function tests is intentionally brief. The largest sections, dealing with the analysis of biochemical constituents, are comprehensive; some of the less common or more difficult procedures, however, such as the determination of protein-bound iodine, are relegated to the bibliography.

The methods listed are those which have been in use by the authors in the Medical Nutrition Laboratory. The careful details, the list of precautions, and the sample calculations included should be of value to those with limited training and experience in such methods. Alternative procedures, however, are rarely included. Such a presentation lacks flexibility, and there are no principles to guide those who might need to modify the procedure in any detail, or to use any apparatus other than that described. Despite a clear exposition of spectrophotometry and of spectrophotometers, filter photometers are barely mentioned, and the emphasis on transmittance rather than optical density is unfortunate. Advantage is not always taken of distinct improvements of original methods (as for example, the Frame, Russel and Wilhelmj modification of Folin's method for amino nitrogen). These are relatively minor drawbacks, however, and those engaged in clinical biochemical work or related fields should find it of great value.

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FRONTAL LOBOTOMY AND AFFECTIVE BEHAVIOR —A Neurophysiological Analysis—John F. Fulton, M.D., Sterling Professor of Physiology, Yale University. W. W. Norton & Company, New York, 1951. 159 pages, $3.00.

This small book is based on the author's Salmon Lectures. Of the 129 pages of text, the general practitioner of medicine will profit most from the last 33, which embrace the rather meager knowledge that is at present available regarding frontal lobe function in man. Certainly every psychiatrist should be familiar with this material, which is becoming part of our basic knowledge of neurophysiology, and upon which psychosurgery rests.

The major portion of the book deals with experimental work in animals, as well as presenting an excellent historical background. It is, however, at times rather slow going, and perhaps with this book the lamentable practice so frequently pursued in reading detective novels, that is, reading the last chapter first, might be recommended.

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PROCEEDINGS OF THE THIRD INTERNATIONAL CONGRESS OF THE INTERNATIONAL SOCIETY OF HEMATOLOGY, Cambridge, England, August 21-25, 1950—Carl V. Moore, U.S.A., Editor-in-Chief. Grune and Stratton, New York, 1951. 593 pages. Cloth bound, $10.00; paper bound, $8.00.

This is the first review volume of *Proceedings* although there have been previous conferences of this organization, in 1946 and in 1948. Included are 176 papers, many only in abstract. The majority of the papers are in English and many of those which are not have English summaries. The text is in four major divisions: I. Anemias and related subjects; II. Immunohematology; III. Leukemia and related diseases; IV. Coagulation, purpura and related subjects. In addition to careful indexing, within each section the papers are arranged according to topic so that reference is easy. Review papers are not included, but the book does contain several papers of general interest, such as Dameshek's on "Acquired Hemolytic Anemia."

Among the many interesting presentations is Owren's suggestion that vitamin B_{12} is not the complete therapy for pernicious anemia. He offered evidence that the level of prothrombin in the blood is not restored to normal by B_{12} therapy. An abnormal hemoglobin has also been demonstrated, and he feels this might be related to the macrocytosis which persists after treatment. Prothrombin and globin in the hemoglobin molecule apparently need a factor other than B_{12} for their normal formation in pernicious anemia.

It is refreshing to see in one volume papers collected from many countries, and to realize what fine work is being done elsewhere. Papers for the most part are in rather limited fields. Consequently, this volume will be of most value to those seriously interested in hematology, either in the clinical, laboratory, or investigative fields. Along with journals in this subject, it should be available for reference to all workers in the field of hematology.

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